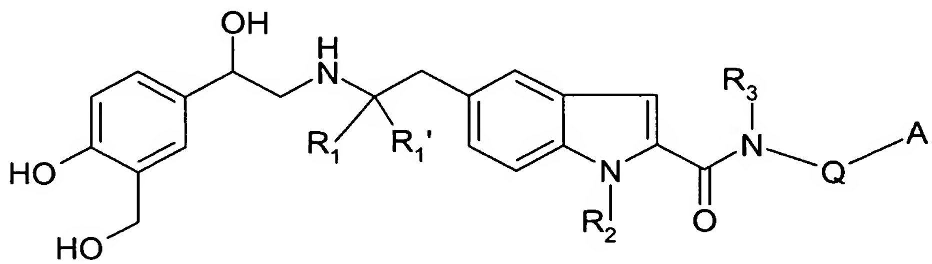
INDOLE DERIVATIVES USEFUL FOR THE TREATMENT OF DISEASES

This invention relates to β2 agonists of the indole derivatives family of general formula :



in which R_1, R_1', R_2, R_3, Q and A have the meanings indicated below,

and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

Adrenoceptors are members of the large G-protein coupled receptor super-family. The adrenoceptor subfamily is itself divided into the α and β subfamilies with the β sub-family being composed of at least 3 receptor sub-types: β1, β2 and β3. These receptors exhibit differential expression patterns in tissues of various systems and organs of mammals. β2 adrenergic (β2) receptors are mainly expressed in smooth muscle cells (e.g. vascular, bronchial, uterine or intestinal smooth muscles), whereas β3 adrenergic receptors are mainly expressed in fat tissues (therefore β3 agonists could potentially be useful in the treatment of obesity and diabetes) and β1 adrenergic receptors are mainly expressed in cardiac tissues (therefore β1 agonists are mainly used as cardiac stimulants).

The pathophysiology and treatments of airway diseases have been extensively reviewed in the literature (for reference see Barnes, P.J. Chest, 1997, 111:2, pp 17S-26S and Bryan, S.A. et al, Expert Opinion on investigational drugs, 2000, 9:1, pp25-42) and therefore only a brief summary will be included here to provide some background information.

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Glucocorticosteroids, anti-leukotrienes, theophylline, cromones, anti-cholinergics and β2 agonists constitute drug classes that are currently used to treat allergic and non-allergic airways diseases such as asthma and chronic obstructive airways disease (COPD). Treatment guidelines for these diseases include both short and long acting inhaled β2 agonists. Short acting, rapid onset β2 agonists are used for "rescue" bronchodilation, whereas, long-acting forms provide sustained relief and are used as maintenance therapy.

Bronchodilation is mediated via agonism of the β2 adrenoreceptor expressed on airway smooth muscle cells, which results in relaxation and hence bronchodilation. Thus, as functional antagonists, β2 agonists can prevent and reverse the effects of all bronchoconstrictor substances, including leukotriene D4 (LTD4), acetylcholine, bradykinin, prostaglandins, histamine and endothelins. Because β2 receptors are so widely distributed in the airway, β2 agonists may also affect other types of cells that play a role in asthma. For example, it has been reported that β2 agonists may stabilize mast cells. The inhibition of the release of bronchoconstrictor substances may be how β2 agonists block the bronchoconstriction induced by allergens, exercise and cold air. Furthermore, β2 agonists inhibit cholinergic neurotransmission in the human airway, which can result in reduced cholinergic-reflex bronchoconstriction.

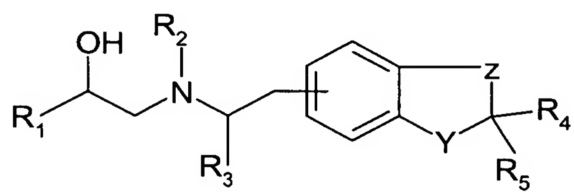
In addition to the airways, it has also been established that β2 adrenoceptors are also expressed in other organs and tissues and thus β2 agonists, such as those described in the present invention, may have application in the treatment of other diseases such as, but not limited to those of the nervous system, premature labor, congestive heart failure, depression, inflammatory and allergic skin diseases, psoriasis, proliferative skin diseases, glaucoma and in conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

However, numerous β2 agonists are limited in their use due to their low selectivity or adverse side-effects driven by high systemic exposure and mainly mediated through action at β2 adrenoreceptors expressed outside the airways

(muscle tremor, tachycardia, palpitations, restlessness). Therefore there is a need for improved agents in this class.

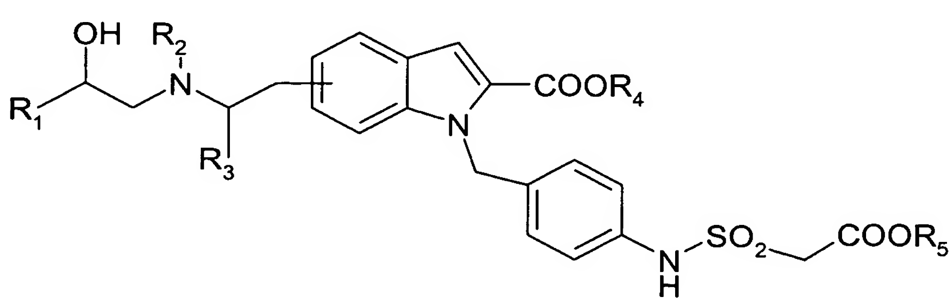
Accordingly, there is still a need for novel β2 agonists that would have an appropriate pharmacological profile, for example in terms of potency. In this context, the present invention relates to novel β2 agonists of the indole derivatives family.

Various indole derivatives have already been synthesised. For example, patent application EP 801 060 discloses dihydroindole derivatives having a selective β3 agonist activity, of formula :



wherein R_1 may be an optionally substituted phenyl (1 to 3 substitutents which may be selected from hydroxyl and hydroxyalkyl), R_2 may be hydrogen, R_3 is hydrogen or alkyl, Z is $-CH_2-$ or $-CH_2-CH_2-$, Y may be $-NR_7-$ (R_7 may be hydrogen or alkyl) and R_4 and R_5 are independently hydrogen, $COOR_6$, $COONR_6R_6$, CHO, COR_6, CH_2OH, $CH_2OCH_2COOR_6$ and $CH_2OCH_2CH_2OR_6$ (R_6 is hydrogen or alkyl).

Patent application EP 822 185 also discloses selective β3 agonists of formula :

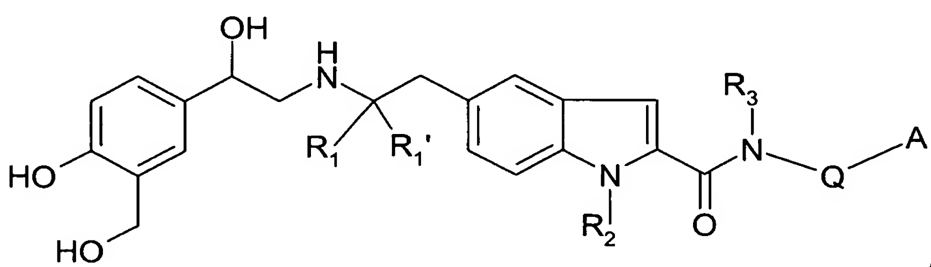


wherein R_1 may be an optionally substituted phenyl with 1 to 3 substitutents selected from hydroxy and hydroxyalkyl, R_2 may be hydrogen, and R_3 may be hydrogen or alkyl optionally independently substituted with one or more halo atoms.

However, none of the indole derivatives synthetised so far have shown β2 agonist activity with high potency (they are all selective β3 agonists) allowing them to be used as efficient drugs in the treatment of the β2-mediated diseases and/or conditions, in particular allergic and non-allergic airways diseases or other diseases such as those previously cited.

It has now been found that the new indole derivatives of formula (1) below are agonists of the β2 receptors, that are particularly useful for the treatment of β2-mediated diseases and/or conditions, by showing good potency, in particular when administered via the inhalation route.

The invention relates to indole derivatives of general formula (1) below :

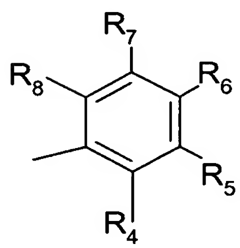


(1)

a) wherein

- Q is a saturated 1 to 4 carbon atom chain substituted with a $(C_1\text{-}C_4)$alkyl;
- R_1 and R_1' are the same or different and are selected from hydrogen and $(C_1\text{-}C_4)$alkyl provided that when R_1 and R_1' are both $C_1\text{-}C_4$ alkyl, they are identical;
- R_2 is selected from hydrogen, $(C_1\text{-}C_4)$alkyl and benzyl optionally substituted with 1, 2 or 3 groups selected from hydroxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo, $O\text{-}CF_3$, $NR_9SO_2(C_1\text{-}C_4)$alkyl, $SO_2NR_9R_{10}$, trifluoromethyl and NR_9R_{10} wherein R_9 and R_{10} are identical or different and are selected from hydrogen and $(C_1\text{-}C_4)$alkyl;

- R_3 is selected from the group consisting of hydrogen and $(C_1\text{-}C_6)$alkyl optionally substituted by a hydroxy;
- A is selected from
  - C_3-C_6 cycloalkyl, optionally substituted with a group selected from hydroxy and $(C_1\text{-}C_4)$alkyl,
  - 5 to 10-membered aromatic heterocyclyl containing from 1 to 3 heteroatoms, identical or different, selected from O, S or N, said heterocyclyl being optionally substituted with a group selected from $(C_1\text{-}C_4)$alkyl and NR_9R_{10} wherein R_9 and R_{10} are the same or different and are selected from H and $(C_1\text{-}C_4)$alkyl or
  - a group



wherein R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, O-CF_3, $NR_9SO_2(C_1\text{-}C_4)$alkyl, $SO_2NR_9R_{10}$, NR_9R_{10}, benzyloxy, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, thio$(C_1\text{-}C_6)$alkyl, halo and trifluoromethyl wherein R_9 and R_{10} are the same or different and are selected from H and $(C_1\text{-}C_4)$alkyl; or

b) wherein

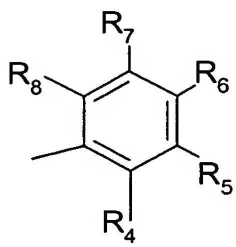
- Q is a single bond or a saturated 1 to 4 carbon atom chain optionally substituted with a $(C_1\text{-}C_4)$alkyl;
- R_1 and R_1' are the same or different and are selected from hydrogen and $(C_1\text{-}C_4)$alkyl provided that when R_1 and R_1' are both C_1-C_4 alkyl, they are identical;
- ;
- R_2 is benzyl optionally substituted with 1, 2 or 3 groups selected from hydroxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo, O-CF_3, $NR_9SO_2(C_1\text{-}C_4)$alkyl, $SO_2NR_9R_{10}$, trifluoromethyl and NR_9R_{10} wherein R_9 and R_{10} are identical or different and are selected from hydrogen and $(C_1\text{-}C_4)$alkyl;

- R_3 is selected from the group consisting of hydrogen and (C_1-C_6)alkyl optionally substituted by a hydroxy; and,
- A is selected from

  - C_3-C_6 cycloalkyl, optionally substituted with a group selected from hydroxy and (C_1-C_4)alkyl,

  - 5 to 6-membered aromatic heterocyclyl containing from 1 to 3 heteroatoms, identical or different, selected from O, S or N, said heterocyclyl being optionally substituted with a group selected from (C_1-C_4)alkyl and NR_9R_{10} wherein R_9 and R_{10} are the same or different and are selected from H and (C_1-C_4)alkyl or

  - a group



  wherein R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, O-CF_3, NR_9SO_2(C_1-C_4)alkyl, $SO_2NR_9R_{10}$, NR_9R_{10}, benzyloxy, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, thio(C_1-C_6)alkyl, halo and trifluoromethyl wherein R_9 and R_{10} are the same or different and are selected from H and (C_1-C_4)alkyl; or

c) wherein

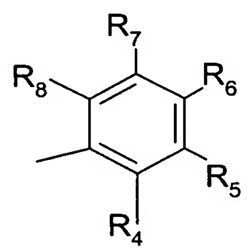
- Q is a single bond or a saturated 1 to 4 carbon atom chain optionally substituted with a (C_1-C_4)alkyl;
- R_1 and R_1' are the same or different and are selected from hydrogen and (C_1-C_4)alkyl provided that when R_1 and R_1' are both C_1-C_4 alkyl, they are identical;
- R_2 is selected from hydrogen, (C_1-C_4)alkyl and benzyl optionally substituted with 1, 2 or 3 groups selected from hydroxy, hydroxy(C_1-C_6)alkyl, (C_1-C_4)alkyl, (C_1-C_6)alkoxy, halo, O-CF_3, NR_9SO_2(C_1-C_4)alkyl, $SO_2NR_9R_{10}$, trifluoromethyl and NR_9R_{10} wherein R_9 and R_{10} are identical or different and are selected from hydrogen and (C_1-C_4)alkyl;

- R_3 is selected from the group consisting of hydrogen and $(C_1\text{-}C_6)$alkyl optionally substituted by a hydroxy; and,
- A is selected from

  - $C_3\text{-}C_6$ cycloalkyl, optionally substituted with a group selected from hydroxy and $(C_1\text{-}C_4)$alkyl,

  - 5 to 10-membered aromatic heterocyclyl containing from 1 to 3 heteroatoms, identical or different, selected from O, S or N, said heterocyclyl being optionally substituted with a group selected from $(C_1\text{-}C_4)$alkyl and NR_9R_{10} wherein R_9 and R_{10} are the same or different and are selected from H and $(C_1\text{-}C_4)$alkyl or

  - a group



wherein one of R_4, R_5, R_6, R_7 and R_8 is selected from O-CF_3, $NR_9SO_2(C_1\text{-}C_4)$alkyl, $SO_2NR_9R_{10}$ and NR_9R_{10} and the others are each independently selected from the group consisting of hydrogen, O-CF_3, $NR_9SO_2(C_1\text{-}C_4)$alkyl, $SO_2NR_9R_{10}$, NR_9R_{10}, benzyloxy, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, thio$(C_1\text{-}C_6)$alkyl, halo and trifluoromethyl wherein R_9 and R_{10} are the same or different and are selected from H and $(C_1\text{-}C_4)$alkyl;

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

In the present invention, the term "potent" means that the compounds of formula (1) show an agonist potency for the β2 receptor, which is less than 10 nM as measured by the cell-based assay described herein.

In the here above general formula (1), $(C_1\text{-}C_4)$alkyl radicals denote a straight-chain or branched group containing 1, 2, 3 or 4 carbon atoms and $(C_1\text{-}$

C_6)alkyl radicals denote a straight-chain or branched group containing 1, 2, 3, 4, 5 or 6 carbon atoms respectively. This also applies if they carry substituents or occur as substituents of other radicals, for example in (C_1-C_6)alkoxy radicals, hydroxy(C_1-C_6)alkyl radicals, thio(C_1-C_6)alkyl radicals etc... . Examples of suitable (C_1-C_6)alkyl radicals are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *n*-hexyl, *iso*-hexyl, 3-methylpentyl etc.... Examples of suitable (C_1-C_6)alkoxy radicals are methoxy, ethoxy, *n*-propyloxy, *iso*-propyloxy, *n*-butyloxy, *iso*-butyloxy, *sec*-butyloxy and *tert*-butyloxy, *n*-pentyloxy, *iso*-pentyloxy, *tert*-pentyloxy, *n*-hexyloxy, *iso*-hexyloxy, 3-methylpentyloxy etc.... Hydroxy(C_1-C_6)alkyl radicals are alkyl radicals substituted by a hydroxy group (-OH). According to a preferred embodiment of said invention, such radicals contain one hydroxy substituent. Examples of suitable hydroxy(C_1-C_6)alkyl radicals are hydroxymethyl, 1-hydroxyethyl or 2-hydroxyethyl. Thio(C_1-C_6)alkyl radicals are alkyl radicals attached to through a –S- atom, i.e. thio(C_1-C_6)alkyl means –S-alkyl. Examples of suitable thio(C_1-C_6)alkyl radicals are thiomethyl, thioethyl, thiopropyl etc...

The term C_3-C_6 cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Examples of suitable 5 to 10-membered aromatic heterocyclyl containing from 1 to 3 heteroatoms selected from O, S or N are thienyl, furanyl, pyranyl, pyrrolyl, imidazolyl, imidazopyridine, pyrazolyl, thiazolyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazyl, triazolyl, isobenzofuranyl, benzofuranyl, benzimidazolyl, benzthiazolyl, indolyl, iso-indolyl, indazolyl, isoquinolyl, quinolyl and naphthyridinyl.

Preferred 5 or 6-membered aromatic heterocyclyl containing from 1 to 3 heteroatoms selected from O, S or N are thiazolyl, pyridyl.

In the general formula (1) according to the present invention, when a radical is mono- or poly-substituted, said substituent(s) can be located at any desired position(s). Also, when a radical is polysubstituted, said substituents can be identical or different.

Finally, halo denotes a halogen atom selected from the group consisting of fluoro, chloro, bromo and iodo in particular fluoro or chloro.

Preferably, R_1 is selected from methyl and ethyl. More preferably, R_1 is methyl.

Preferably, R_1' is selected from H and methyl. More preferably R_1' is H.

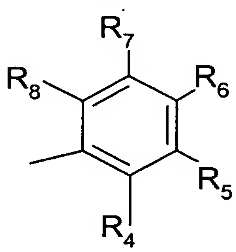
Preferably, R_2 is selected from H, methyl, ethyl and benzyl.

Preferably, R_3 is selected from H and methyl, more preferably R_3 is H.

Preferably, Q is selected from $-CH_2-$, CH_2-CH_2, and $-CH(CH_3)-$.

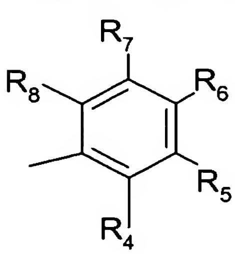
Preferably, when A is phenyl, at least 2 of R_4, R_5, R_6, R_7 and R_8 are hydrogen.

Preferably, A is selected from C_3-C_6 cycloalkyl, 5 or 6-membered aromatic heterocyclyl containing 1 or 2 heteroatoms selected from O, S or N and a group



wherein R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, $O-CF_3$, $SO_2NR_9R_{10}$, benzyloxy, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy$(C_1$-$C_6)$alkyl, thio$(C_1$-$C_6)$alkyl, halo and trifluoromethyl wherein R_9 and R_{10} are the same or different and are selected from H and $(C_1$-$C_4)$alkyl;

Preferably, A is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, thiazolyl, pyridyl and a group



wherein 2 of R_4, R_5, R_6, R_7 and R_8 are hydrogen and the others are selected from chloro, fluoro, methyl, hydroxy, methoxy, ethoxy, benzyloxy, trifluoromethyl, trifluoromethyloxy, thiomethyl and $SO_2NR_9R_{10}$ wherein R_9 and R_{10} are the same or different and are selected from hydrogen or $(C_1\text{-}C_4)$alkyl

Preferred compounds according to the invention are compounds of formula (1)

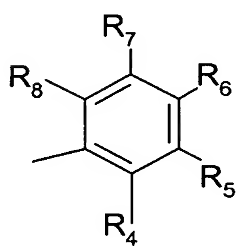
a) wherein

- Q is a saturated 1 to 4 carbon atom chain substituted with a $(C_1\text{-}C_4)$alkyl;
- R_1 is $(C_1\text{-}C_4)$alkyl and R_1' is H.
- R_2 is selected from hydrogen, $(C_1\text{-}C_4)$alkyl and benzyl;
- R_3 is selected from the group consisting of hydrogen and $(C_1\text{-}C_6)$alkyl;
- A is selected from

  - C_3-C_6 cycloalkyl,

  - 5 or 6-membered aromatic heterocyclyl containing from 1 to 3 heteroatoms, identical or different, selected from O, S or N, and,

  - a group



  wherein R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, O-CF_3, $NR_9SO_2(C_1\text{-}C_4)$alkyl, $SO_2NR_9R_{10}$, NR_9R_{10}, benzyloxy, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, thio$(C_1\text{-}C_6)$alkyl, halo and trifluoromethyl wherein R_9 and R_{10} are the same or different and are selected from H and $(C_1\text{-}C_4)$alkyl; or

b) wherein

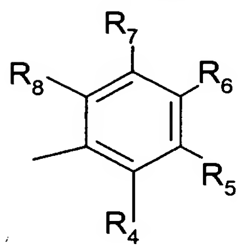
- Q is a single bond or a saturated 1 to 4 carbon atom chain optionally substituted with a $(C_1\text{-}C_4)$alkyl;
- R_1 is selected from hydrogen and $(C_1\text{-}C_4)$alkyl and R_1' is H;
- R_2 is benzyl;
- R_3 is selected from the group consisting of hydrogen and $(C_1\text{-}C_6)$alkyl

- A is selected from

  - C_3-C_6 cycloalkyl,

  - 5 or 6-membered aromatic heterocyclyl containing from 1 to 3 heteroatoms, identical or different, selected from O, S or N, and,

  - a group



wherein R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, O-CF_3, $NR_9SO_2(C_1$-$C_4)$alkyl, $SO_2NR_9R_{10}$, NR_9R_{10}, benzyloxy, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy$(C_1$-$C_6)$alkyl, thio$(C_1$-$C_6)$alkyl, halo and trifluoromethyl wherein R_9 and R_{10} are the same or different and are selected from H and $(C_1$-$C_4)$alkyl; or

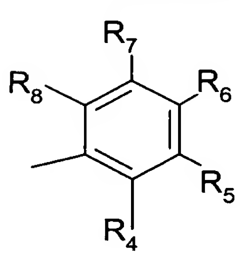
c) wherein

- Q is a single bond or a saturated 1 to 4 carbon atom chain optionally substituted with a $(C_1$-$C_4)$alkyl;
- R_1 is selected from hydrogen and $(C_1$-$C_4)$alkyl and R_1' is H;
- R_2 is selected from hydrogen, $(C_1$-$C_4)$alkyl and benzyl;
- R_3 is selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl ;
- A is selected from

  - C_3-C_6 cycloalkyl;

  - 5 or 6-membered aromatic heterocyclyl containing from 1 to 3 heteroatoms, identical or different, selected from O, S or N;

  - a group



wherein one of R_4, R_5, R_6, R_7 and R_8 is selected from O-CF_3, $NR_9SO_2(C_1$-$C_4)$alkyl, $SO_2NR_9R_{10}$ and NR_9R_{10} and the others are each independently selected from the group consisting of hydrogen, O-CF_3, $NR_9SO_2(C_1$-$C_4)$alkyl, $SO_2NR_9R_{10}$, NR_9R_{10}, benzyloxy, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy$(C_1$-$C_6)$alkyl, thio$(C_1$-$C_6)$alkyl, halo and trifluoromethyl wherein R_9 and R_{10} are the same or different and are selected from H and $(C_1$-$C_4)$alkyl;

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

Further preferred compounds according to the invention are compounds of formula (1)

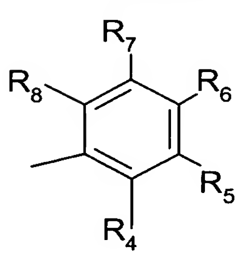
a) wherein

- Q is –CH(CH_3)-;
- R_1 is selected from methyl or ethyl and R_1' is H;
- R_2 is selected from hydrogen, methyl, ethyl and benzyl;
- R_3 is selected from hydrogen and methyl;
- A is selected from

  - C_3-C_6 cycloalkyl, preferably cyclopropyl, cyclopentyl or cyclohexyl;

  - 5 or 6-membered aromatic heterocyclyl containing 1 or 2 heteroatoms, identical or different, selected from S or N, preferably pyridyl or thiazolyl and,

  - a group



wherein R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, O-CF_3, $SO_2NR_9R_{10}$, benzyloxy, hydroxy, methyl, methoxy, ethoxy, thiomethyl, halo and trifluoromethyl wherein R_9

and R_{10} are the same or different and are selected from hydrogen and methyl; or,

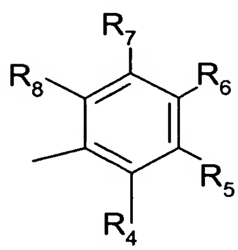
b) wherein

- Q is selected from $-CH_2-$, CH_2-CH_2, and $-CH(CH_3)-$;
- R_1 is selected from methyl or ethyl and R_1' is H;
- R_2 is benzyl;
- R_3 is selected from hydrogen and methyl;
- A is selected from

  - C_3-C_6 cycloalkyl, preferably cyclopropyl, cyclopentyl or cyclohexyl;

  - 5 or 6-membered aromatic heterocyclyl containing 1 or 2 heteroatoms, identical or different, selected from S or N, preferably pyridyl or thiazolyl and,

  - a group



wherein R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, O-CF_3, $SO_2NR_9R_{10}$, benzyloxy, hydroxy, methyl, methoxy, ethoxy, thiomethyl, halo and trifluoromethyl wherein R_9 and R_{10} are the same or different and are selected from hydrogen and methyl; or

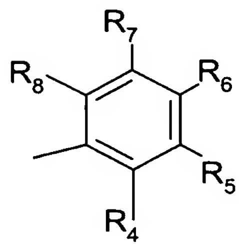
c) wherein

- Q is selected from $-CH_2-$, CH_2-CH_2, and $-CH(CH_3)-$;
- R_1 is selected from methyl or ethyl and R_1' is H;
- R_2 is selected from hydrogen, methyl, ethyl and benzyl;
- R_3 is selected from hydrogen and methyl;
- A is selected from

  - C_3-C_6 cycloalkyl, preferably cyclopropyl, cyclopentyl or cyclohexyl;

- 5 or 6-membered aromatic heterocyclyl containing 1 or 2 heteroatoms, identical or different, selected from S or N, preferably pyridyl or thiazolyl and,

- a group



wherein one of R_4, R_5, R_6, R_7 and R_8 is selected from O-CF_3 and $SO_2NR_9R_{10}$ and the others are each independently selected from the group consisting of hydrogen, O-CF_3, $SO_2NR_9R_{10}$, benzyloxy, hydroxy, methyl, methoxy, ethoxy, thiomethyl, halo and trifluoromethyl wherein R_9 and R_{10} are the same or different and are selected from hydrogen and methyl.

More preferred compounds according to the invention are compounds of formula (1)

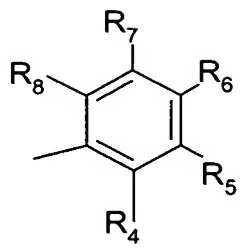
a) wherein

- Q is –CH(CH_3)-;
- R_1 is selected from methyl or ethyl and R_1' is H;
- R_2 is selected from hydrogen, methyl, ethyl and benzyl;
- R_3 is hydrogen;
- A is selected from

- C_3-C_6 cycloalkyl, preferably cyclopropyl, cyclopentyl or cyclohexyl;

- 5 or 6-membered aromatic heterocyclyl containing 1 or 2 heteroatoms, identical or different, selected from S or N, preferably pyridyl or thiazolyl and,

- a group



wherein R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, O-CF_3, $SO_2NR_9R_{10}$ and methoxy wherein R_9 and R_{10} are the same or different and are selected from hydrogen and methyl; or,

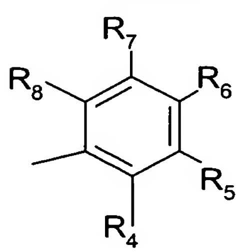
b) wherein

- Q is selected from –CH_2- and –$CH(CH_3)$-;
- R_1 is selected from methyl or ethyl and R_1' is H;
- R_2 is benzyl;
- R_3 is hydrogen;
- A is selected from

  - C_3-C_6 cycloalkyl, preferably cyclopropyl, cyclopentyl or cyclohexyl;

  - 5 or 6-membered aromatic heterocyclyl containing 1 or 2 heteroatoms, identical or different, selected from S or N, preferably pyridyl or thiazolyl and,

  - a group



wherein R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, O-CF_3, $SO_2NR_9R_{10}$ and methoxy wherein R_9 and R_{10} are the same or different and are selected from hydrogen and methyl; or,

c) wherein

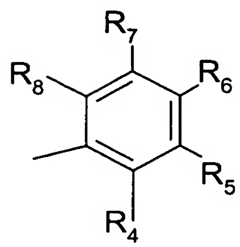
- Q is selected from –CH_2- and –$CH(CH_3)$-;
- R_1 is selected from methyl or ethyl and R_1' is H;

- R_2 is selected from hydrogen, methyl, ethyl and benzyl;
- R_3 is hydrogen;
- A is selected from

  - C_3-C_6 cycloalkyl, preferably cyclopropyl, cyclopentyl or cyclohexyl;

  - 5 or 6-membered aromatic heterocyclyl containing 1 or 2 heteroatoms, identical or different, selected from S or N, preferably pyridyl or thiazolyl and,

  - a group



wherein one of R_4, R_5, R_6, R_7 and R_8 is selected from O-CF_3 and $SO_2NR_9R_{10}$ and the others are each independently selected from the group consisting of hydrogen, O-CF_3, $SO_2NR_9R_{10}$ and methoxy wherein R_9 and R_{10} are the same or different and are selected from hydrogen and methyl.

Particularly preferred are the indole derivatives of the formula (1) as described in the Examples section hereafter, i.e. :

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-N-(2-trifluoromethoxybenzyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-[(1S)-1-phenylethyl]-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-(3-trifluoromethoxyphenylethyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-(pyridin-2-ylmethyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-(cyclopropylmethyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-[(1R)-1-phenylethyl]-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-(thiazol-2-ylmethyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-(cyclobutylmethyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-(cyclopentylmethyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-(cyclohexylmethyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-(4-methylsulfamoylbenzyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-(4-sulfamoylbenzyl)-1H-indole-2-carboxamide;

1-Benzyl-5-[(2R)-2-({(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl) ethyl}amino)propyl}-N-(2-methoxybenzyl)-1H-indole-2-carboxamide;

1-Benzyl-5-[(2R)-2-({(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl) ethyl}amino)propyl}-N-[(1R)-1-phenylethyl]-1H-indole-2-carboxamide;

1-Ethyl-5-[(2R)-2-({(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl) ethyl}amino)propyl}-N-[(1R)-2-phenylethyl)-1H-indole-2-carboxamide;

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-N-[(1R)-1-phenylethyl)-1-methyl-1H-indole-2-carboxamide;

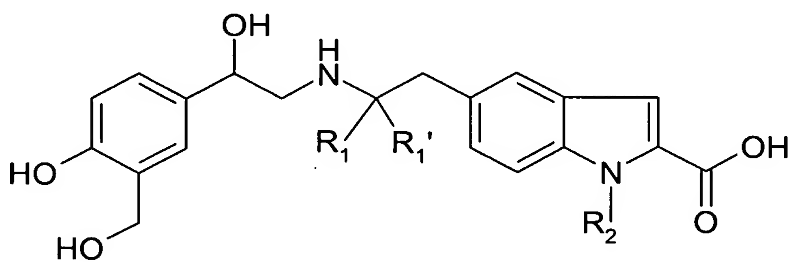
1-Benzyl-5-[(2R)-2-({(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl) ethyl}amino)propyl}-N-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,

5-[(2R)-2-({(2R)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)butyl}-N-[(1R)-1-phenylethyl]-1H-indole-2-carboxamide, and,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)butyl}-*N*-[3-methyl-pyridin-2-ylmethyl]-1H-indole-2-carboxamide.

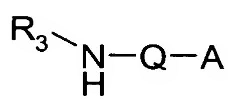
The indole derivatives of the formula (1) can be prepared using conventional procedures such as by the following illustrative methods in which R_1, R_2, R_3, Q and A are as previously defined for the indole derivatives of the formula (1) unless otherwise stated.

The indole derivatives of the formula (1) may be prepared by coupling an acid of formula (2) :



(2)

with an amine of formula (3) :

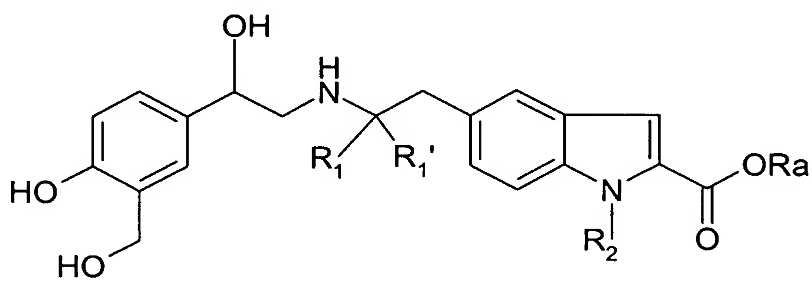


wherein R_3, Q and A are as previously defined. The coupling is generally carried out in an excess of said amine as an acid receptor, with a conventional coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or *N,N'*-dicyclohexylcarbodiimide), optionally in the presence of a catalyst (e.g. 1-hydroxybenzotriazole hydrate or 1-hydroxy-7-azabenzotriazole), and optionally in the presence of a tertiary amine base (e.g. N-methylmorpholine, triethylamine or diisopropylethylamine). The reaction may be undertaken in a suitable solvent such as pyridine, dimethylformamide,

tetrahydrofuran, dimethylsulfoxide, dichloromethane or ethyl acetate, and at temperature comprised between 10°C and 40°C (room temperature). It may also be necessary to deprotect one of the substituents to furnish the desired compound. This may be achieved by, in the case of a benzyl protecting group, hydrogenation typically at 15-60 psi in a solvent such as methanol or ethanol at ambient or up to 50 °C

Said amine (3) is either commercially available or may be prepared by conventional methods well known to the one skilled in the art (e.g. reduction, oxidation, alkylation, protection, deprotection etc...) from commercially available material.

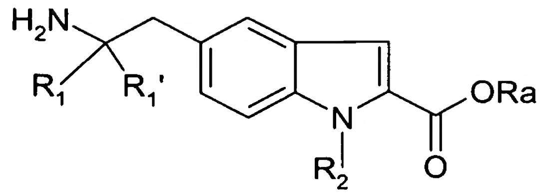
The acid of formula (2) may be prepared from the corresponding ester of formula (4) :



(4)

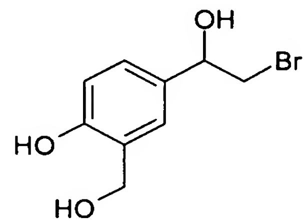
wherein Ra is a suitable acid protecting group, preferably a $(C_1\text{-}C_4)$alkyl group, which includes, but is not limited to, methyl and ethyl, according to any method well-known to the one skilled in the art to prepare an acid from an ester, without modifying the rest of the molecule. For example, the ester may be hydrolysed by treatment with aqueous acid or base (e.g. hydrogen chloride, potassium hydroxide, sodium hydroxide or lithium hydroxide), optionally in the presence of a solvent or mixture of solvents (e.g. water, 1,4-dioxan, tetrahydrofuran/water), at a temperature comprised between 20°C and 100°C, for a period of 1 to 40 hours.

The ester of formula (4) may be prepared by reaction of an amine of formula (5) :



(5)

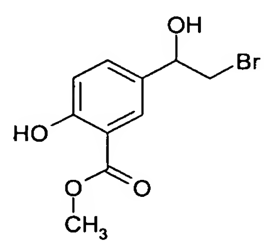
wherein Ra is as previously defined,
with a bromide of formula (6) :



(6)

In a typical procedure, the amine of formula (5) is reacted with a bromide of formula (6) optionally in the presence of a solvent or mixture of solvents (e.g. dimethyl sulfoxide, toluene, N,N-dimethylformamide), optionally in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine) at a temperature comprised between 80°C and 120°C, for 12 to 48 hours.

The bromide of formula (6) may be prepared from the ester of formula (7) :



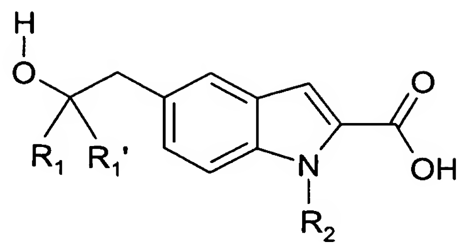
(7)

according to any method well-known to the one skilled in the art to prepare an alcohol from an ester, without modifying the rest of the molecule.

In a typical procedure, the ester of formula (7) is reduced with borane methylsulfide complex in tetrahydrofuran at a reflux for a period of 2 hours.

The alcohol of formula (7) may be prepared as either the *(R)* or *(S)* enantiomer according to methods well described in the literature (Tetrahedron Letters 1994, 35(50), 9375).

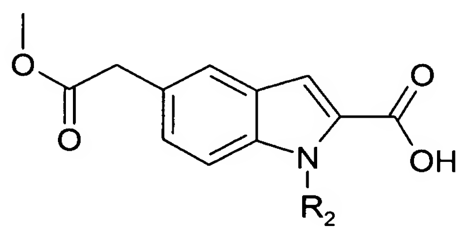
The amine of formula (5) wherein R_1 and R'_1 are C_1-C_4 alkyl may be prepared from the tertiary alcohol of formula (13).



(13)

Said tertiary alcohol of formula (13) is treated with an alkyl nitrile (e.g. acetonitrile, chloroacetonitrile) in the presence of an acid (e.g. sulphuric acid, acetic acid) to give a protected intermediate which in turn is cleaved using standard methodology for cleaving nitrogen protecting group such as those mentioned in textbooks, to give the amine of formula (5) wherein R_1 and R_1' are C_1-C_4 alkyl.

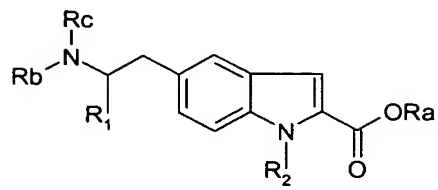
The tertiary alcohol of formula (13) may be prepared from the ketone of formula (14):



(14)

In a typical procedure, the ketone of formula (14) is reacted with an "activated" alkyl (organometallic alkyl such as R_1MgBr , R_1MgCl or R^1Li) to give the corresponding tertiary alcohol of formula (13). This organometallic addition is generally undertaken in a suitable solvent such as tetrahydrofuran, ether, cyclohexane or 1,4-dioxane, at a temperature comprised between 10°C and 40°C (room temperature) for 1 to 24 hours

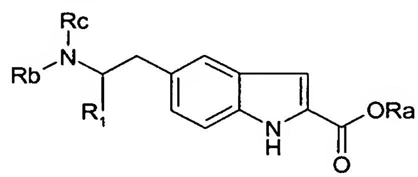
The amine of formula (5) wherein R_1' is hydrogen may be prepared as either the *(R)* or *(S)* enantiomer from the corresponding protected indole of formula (8) :



(8)

wherein Ra is as previously defined and Rb and Rc represent any suitable substituents so that HNRbRc is a chiral amine (for example, Rb may be hydrogen and Rc may be a α-methylbenzyl group), provided that the bonds between N and Rb and N and Rc can be easily cleaved to give the free amine of formula (5) using standard methodology for cleaving nitrogen protecting groups, such as that found in the text book (see for example T.W. GREENE, Protective Groups in Organic Synthesis , A. Wiley-Interscience Publication, 1981).

The amine of formula (8) as either (R) or (S) enantiomer may be prepared by alkylation of a compound of formula (9) :

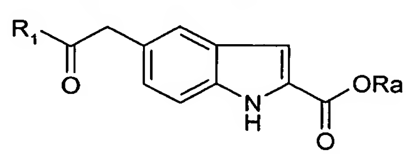


(9)

wherein R_1, Ra, Rb and Rc are as previously defined.

In a typical procedure, the compound of formula (9) may be alkylated with a suitable alkylating agent (e.g. R_2Br or R_2I) in the presence of a suitable base (e.g. sodium hydride). The reaction is generally done in a solvent such as tetrahydrofuran or dimethylformamide, at a temperature comprised between-10°C and 80°C for 1 to 16 hours. The product is then converted to the hydrochloride salt and selectively crystallised from a suitable solvent or mixture of solvents (e.g. isopropanol, ethanol, methanol, diisopropyl ether or diisopropyl ether/methanol) to give the chiral product of formula (8) or its enantiomer if the opposite enantiomer of the amine NHRbRc is used.

The compound of formula (9) may be prepared by reaction of an amine of formula HNRbRc with a ketone of formula (10) :

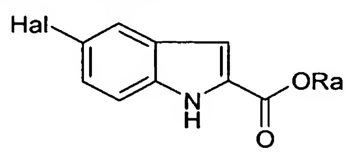


(10)

wherein R_1, Ra, Rb and Rc are as previously defined.

In a typical procedure, the reaction of the ketone of formula (10) with the amine of formula HNRbRc leads to a chiral intermediate which is in turn reduced by a suitable reducing agent (e.g. sodium cyanoborohydride of formula $NaCNBH_3$ or sodium triacetoxyborohydride of formula $Na(OAc)_3BH$) optionally in the presence of a drying agent (e.g. molecular sieves, magnesium sulfate) and optionally in the presence of an acid catalyst (e.g. acetic acid) to give the amine of formula (9). The reaction is generally done in a solvent such as tetrahydrofuran or dichloromethane at a temperature comprised between 20°C and 80°C for 3 to 72 hours.

The ketone of formula (10) may be prepared by palladium mediated coupling of an aryl halide of formula (11) :

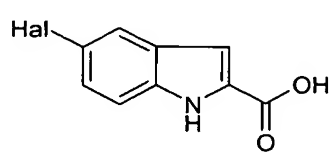


(11)

wherein Ra is as previously defined and Hal represents an halogen atom, which includes, but is not limited to bromo and iodo,
with an enolate or enolate equivalent.

In a typical procedure, the aryl halide of formula (11) is reacted with a tin enolate generated in-situ by treatment of isoprenyl acetate with tri-n-butyltin methoxide of formula Bu_3SnOMe in the presence of a suitable palladium catalyst (palladium acetate/ tri-ortho-tolylphosphine of formula $Pd(OAc)_2/P(o\text{-}Tol)_3$) in a non-polar solvent (e.g. toluene, benzene, hexane). Preferably, the reaction is carried out at a temperature comprised between 80°C and 110°C for 6 to 16 hours.

The aryl halide of formula (11) may be obtained by esterification of the corresponding acid of formula (12) :



(12)

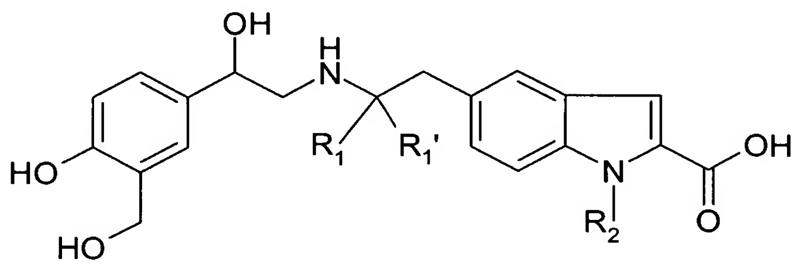
wherein Hal is as previously defined,

according to any method well-known to the one skilled in the art to prepare an ester from an acid, without modifying the rest of the molecule.

In a typical procedure, the acid of formula (12) is reacted with an alcoholic solvent of formula RaOH, wherein Ra is as previously defined, in the presence of an acid such as hydrogen chloride at a temperature between 10°C and 40°C (room temperature) for 8 to 16 hours.

The acid of formula (12) is a commercial product.

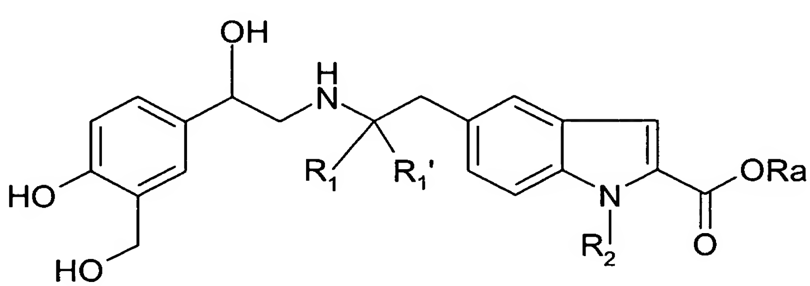
The invention also relates to an intermediate of formula (2):



(2)

wherein R_1 and R_1' are the same or different and are selected from hydrogen and $(C_1\text{-}C_4)$alkyl and R_2 is benzyl optionally substituted with 1, 2 or 3 groups selected from hydroxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo, O-CF_3, $NR_9SO_2(C_1\text{-}C_4)$alkyl, $SO_2NR_9R_{10}$, trifluoromethyl and NR_9R_{10} wherein R_9 and R_{10} are identical or different and are selected from hydrogen and $(C_1\text{-}C_4)$alkyl.

The invention also relates to an intermediate of formula (4):



(4)

wherein R_1 and R_1' are the same or different and are selected from hydrogen and $(C_1\text{-}C_4)$alkyl, R_2 is benzyl optionally substituted with 1, 2 or 3 groups selected from hydroxy, methoxy, $(C_1\text{-}C_4)$alkyl and NR_9R_{10} wherein R_9 and R_{10}

are identical or different and are selected from hydrogen and (C_1-C_4)alkyl, and Ra is a suitable acid protecting group selected from (C_1-C_4)alkyl groups.

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

For some of the steps of the here above described process of preparation of the indole derivatives of formula (1), it can be necessary to protect the potential reactive functions that are not wished to react, and to cleave said protecting groups in consequence. In such a case, any compatible protecting radical can be used. In particular methods of protection and deprotection such as those described by T.W. GREENE (*Protective Groups in Organic Synthesis*, A. Wiley-Interscience Publication, 1981) or by P. J. Kocienski (*Protecting groups*, Georg Thieme Verlag, 1994), can be used.

Also, the indole derivatives of formula (1) as well as intermediate for the preparation thereof can be purified according to various well-known methods, such as for example crystallization or chromatography.

The indole derivatives of formula (1) may also be optionally transformed into pharmaceutically acceptable salts. In particular, these pharmaceutically acceptable salts of the indole derivatives of the formula (1) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from mineral or organic non-toxic acids which form non-toxic salts. Suitable examples of these acid addition salts are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate,

ethanesulphonate, benzenesulphonate, *p*-toluenesulphonate, pamoate and xinafoate salts.

Suitable base salts are formed from bases, which form non-toxic salts, such as alkali metal salts, earth metal salts or addition salts with ammonia and physiologically tolerable organic amines. Suitable examples of these base salts are the sodium, potassium, aluminium, calcium, magnesium, zinc or ammonium salts as well as addition salts with triethylamine, ethanolamine, diethanolamine, trimethylamine, methylamine, propylamine, diisopropylamine, N,N-dimethylethanolamine, benzylamine, dicyclohexylamine, N-benzyl-β-phenethylamine, N,N'-dibenzylethylenediamine, diphenylenediamine, quinine, choline, arginine, lysine, leucine, dibenzylamine, tris(2-hydroxyethyl)amine, or α,α,α-tris(hydroxymethyl)methylamine.

Compounds which contain both acidic groups and basic groups can also be present in the form of internal salts or betaines, which are also included by the present invention. For a review on suitable salts see Berge *et al.*, *J. Pharm. Sci.*, 1977, 66, p. 1-19.

Salts can generally be obtained from the indole derivatives of the formula (1) according to customary procedures known to the person skilled in the art, for example by combining with an organic or inorganic acid or base solvent or dispersant, or alternatively from other salts by anion exchange or cation exchange. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The indole derivatives of the formula (1) can also be present in stereoisomeric forms. If the indole derivatives of the formula (1) contain one or more centres of asymmetry, these can independently of one another have the (S) configuration or the (R) configuration. The invention includes all possible stereoisomers of the indole derivatives of the formula (1), for example enantiomers and diastereomers, and mixtures of two or more stereoisomeric forms, for example mixtures of enantiomers and/or diastereomers, in all ratios. The invention thus relates to enantiomers in enantiomerically pure form, both

as levorotatory and dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. The invention likewise relates to diastereomers in diastereomerically pure form and in the form of mixtures in all ratios. In the presence of cis/trans isomerism, the invention relates to both the cis form and the trans form and mixtures of these forms in all ratios. Individual stereoisomers can be prepared, if desired, by use of stereochemically homogeneous starting substances in the synthesis, by stereoselective synthesis or by separation of a mixture according to customary methods, for example by chromatography, crystallization or by chromatography on chiral phases. If appropriate, derivatization can be carried out before separation of stereoisomers. A stereoisomer mixture can be separated at the stage of the indole derivatives of the formula (1) or at the stage of a starting substance or of an intermediate in the course of the synthesis.

According to one aspect of the present invention, the (R,R)-stereoisomer is generally preferred.

The compounds of the formula (1) according to the invention can moreover contain mobile hydrogen atoms, i.e. be present in various tautomeric forms. The present invention also relates to all tautomers of the compounds of the formula (1).

The present invention furthermore includes other types of derivatives of indole derivatives of the formula (1), for example, solvates such as hydrates and polymorphs, i.e. the various different crystalline structures of the indole derivatives according to the present invention.

The present invention also includes all suitable isotopic variations of the indole derivatives of the formula (1) or a pharmaceutically acceptable salt thereof. An isotopic variation of the indole derivatives of the formula (1) or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into the indole derivatives of the formula (1)

and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, sulphur, fluorine and chlorine such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of the indole derivatives of the formula (1) and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the indole derivatives of the formula (1) and pharmaceutically acceptable salts thereof of this invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations sections hereafter using appropriate isotopic variations of suitable reagents.

According to a further aspect, the present invention concerns mixtures of indole derivatives of the formula (1), as well as mixtures with or of their pharmaceutically acceptable salts, solvates, isomeric forms and/or isotope forms.

According to the present invention, all the here above mentioned forms of the indole derivatives of formula (1) except the pharmaceutically acceptable salts (i.e. said solvates, isomeric forms, tautomers and isotope forms), are defined as “derived forms” of the indole derivatives of formula (1) in what follows (including the claims).

The indole derivatives of formula (1), their pharmaceutically acceptable salts and/or derived forms, are valuable pharmaceutically active compounds, which are suitable for the therapy and prophylaxis of numerous disorders in which the β2 receptor is involved or in which agonism of this receptor may induce benefit, in particular the allergic and non-allergic airways diseases but

also in the treatment of other diseases such as, but not limited to those of the nervous system, premature labor, congestive heart failure, depression, inflammatory and allergic skin diseases, psoriasis, proliferative skin diseases, glaucoma and in conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

The indole derivatives of formula (1) and their pharmaceutically acceptable salts and derived forms as mentioned above can be administered according to the invention to animals, preferably to mammals, and in particular to humans, as pharmaceuticals for therapy and/or prophylaxis. They can be administered per se, in mixtures with one another or in the form of pharmaceutical preparations which as active constituent contain an efficacious dose of at least one indole derivative of the formula (1), its pharmaceutically acceptable salts and/or derived forms, in addition to customary pharmaceutically innocuous excipients and/or additives.

Thus, the present invention also relates to compositions containing an indole derivative of formula (1) and/or their pharmaceutically acceptable salts and/or derived forms, together with customary pharmaceutically innocuous excipients and/or additives. Such compositions are prepared according to well-known methods compatible with the standard pharmaceutical practice. Said compositions generally contain from 0.5 % to 60 % in weight of the active compound and from 40 % to 99.5 % in weight of excipients and/or additives. According to the present invention, said excipients and/or additives are agents well known to the artisan for providing favourable properties in the final pharmaceutical composition. Typical excipients and/or additives include, but are by no means limited to, acidifying and alkalizing agents, aerosol propellants, anti-microbial agents (including anti-bacterial, anti-fungal and anti-protozoal agents), antioxidants, buffering agents, chelating agents, dispersing agents, suspending agents, emollients, emulsifying agents, preservatives, sequestering agents, solvents, stabilizers, stiffening agents, sugars, surfactants and flavouring agents. Furthermore, said compositions are prepared in a form compatible for the intended route of administration, which is used for any given

patient, as well as appropriate to the disease, disorder or condition for which any given patient is being treated. Suitable routes of administration that can be envisaged are for example the topical, oral, inhaled, rectal, intra-veinous, intra-arterial, intra-peritoneal, intra-thecal, intra-ventricular, intra-urethral, intra-sternal, intra-cranial, intra-muscular, subcutaneous or ocular routes. In the present case, the inhalation route is preferred.

When an administration by the oral route is intended, the indole derivatives of formula (1), their pharmaceutically acceptable salts and/or their derived forms, can be administered in the form of tablets, capsules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The indole derivatives of formula (1), their pharmaceutically acceptable salts and/or their derived forms, may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations of the indole derivatives of formula (1), their pharmaceutically acceptable salts and/or their derived forms, may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

As a general example, a formulation of the tablet could typically contain between about 0.001 mg and 5000 mg of active compound whilst tablet fill weights may range from 50 mg to 5000 mg. The tablets may be manufactured

by a standard process, for example by direct compression or by a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the indole derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The indole derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, can also be administered by injection, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion or needleless injection techniques. For such administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of such formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For both oral administration and injection to human patients, the daily dosage level of the indole derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, will usually be from 0.001 mg/kg to 1000 mg/kg (in single or divided doses).

The indole derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, can also be administered by inhalation and are conveniently delivered in the form of a dry powder inhaler or

an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A™) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA™), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of an indole derivative of the formula (1) and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 0.001 mg to 10 mg of an indole derivative of the formula (1) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 0.001 mg to 40 mg, which may be administered in a single dose or, more usually, in divided doses throughout the day.

The indole derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, can also be administered topically, or transdermally, in the form of creams, gels, suspensions, lotions, ointments, dusting powders, sprays, foams, mousses, drug-incorporated dressings, solutions, sponges, fibres, microemulsions, films, skin patches, ointments such as petrolatum or white soft paraffin based ointments or via a skin patch or other device. Penetration enhancers may be used, and the compound may be used in combination with cyclodextrins. In addition, the compound may be delivered using iontophoresis, electropration, phonophoresis or sonophoresis. They could be administered directly onto a wound site. They could be incorporated into a coated suture. For example they can be incorporated into a lotion or cream

consisting of an aqueous or oily emulsion of mineral oils, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, water, polyethylene glycols and/or liquid paraffin, or they can be incorporated into a suitable ointment consisting of one or more of the following : mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water, or as hydrogel with cellulose or polyacrylate derivatives or other viscosity modifiers, or as a dry powder or liquid spray or aerosol with butane/propane, HFA, CFC, CO_2 or other suitable propellant, optionally also including a lubricant such as sorbitan trioleate, or as a drug-incorporated dressing either as a tulle dressing, with white soft paraffin or polyethylene glycols impregnated gauze dressings or with hydrogel, hydrocolloid, alginate or film dressings.

For topical administration to human patients with acute/surgical wounds or scars, the daily dosage level of the compounds, in suspension or other formulation, could be from 0.001 to 50 mg/ml, preferably from 0.03 to 30 mg/ml. The dosage will vary with the size of the wound, whether or not the wound is open or closed or partially closed, and whether or not the skin is intact.

Alternatively, the indole derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, can be rectally administered, for example in the form of a suppository of a gel, although other forms can be considered.

They may also be administered by the ocular route, in particular for ocular scarring. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

The various pharmaceutical formulations as decribed here above are also detailed in "Pharmacie galénique" from A. Lehir (Ed. Mason, 1992, 2nd edition).

The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight, health state and sex of the patient as well as the severity of the disease, disorder or condition to treat, the optional combination with other treatment(s), the response of the particular patient and in general any factor peculiar to the concerned disease, disorder or condition and to the patient. Thus, the daily dose in human may usually contain from 0.001 mg to 5000 mg of active compound for administration singly or two or more at a time, as appropriate. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

According to the present invention, the indole derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. α-, β- and γ-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

According to another embodiment of the present invention, the indole derivatives of the formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, can also be used as a combination with one or more additional therapeutic agents to be co-administered to a patient to obtain some particularly desired therapeutic end result. The second and more additional therapeutic agents may also be an indole derivative of the formula

(1), or pharmaceutically acceptable salts, derived forms or compositions thereof, or one or more β2 agonists known in the art. More typically, the second and more therapeutic agents will be selected from a different class of therapeutic agents.

As used herein, the terms “co-administration”, “co-administered” and “in combination with”, referring to the indole derivatives of formula (1) and one or more other therapeutic agents, is intended to mean, and does refer to and include the following :

- simultaneous administration of such combination of indole derivative(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient,
- substantially simultaneous administration of such combination of indole derivative(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient,
- sequential administration of such combination of indole derivative(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and
- sequential administration of such combination of indole derivative(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner whereupon they are

concurrently, consecutively, and/or overlapingly administered at the same and/or different times by said patient,

where each part may be administered by either the same or different route.

Suitable examples of other therapeutic agents which may be used in combination with the indole derivatives of the formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, include, but are by no means limited to :

(a) 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists,
(b) Leukotriene antagonists (LTRAs) including antagonists of LTB_4, LTC_4, LTD_4, and LTE_4,
(c) Histamine receptor antagonists including H1 and H3 antagonists,
(d) α_1- and α_2-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,
(e) muscarinic M3 receptor antagonists or anticholinergic agents,
(f) PDE inhibitors, e.g. PDE3, PDE4 and PDE5 inhibitors,
(g) Theophylline,
(h) Sodium cromoglycate,
(i) COX inhibitors both non-selective and selective COX-1 or COX-2 inhibitors (NSAIDs),
(j) Oral and inhaled glucocorticosteroids,
(k) Monoclonal antibodies active against endogenous inflammatory entities,
(l) Anti-tumor necrosis factor (anti-TNF-α) agents,
(m)Adhesion molecule inhibitors including VLA-4 antagonists,
(n) Kinin-B_1 - and B_2 -receptor antagonists,
(o) Immunosuppressive agents,
(p) Inhibitors of matrix metalloproteases (MMPs),
(q) Tachykinin NK_1, NK_2 and NK_3 receptor antagonists,
(r) Elastase inhibitors,
(s) Adenosine A2a receptor agonists,
(t) Inhibitors of urokinase,

(u) Compounds that act on dopamine receptors, e.g. D2 agonists,
(v) Modulators of the NFκβ pathway, e.g. IKK inhibitors,
(w) Agents that can be classed as mucolytics or anti-tussive, and
(x) Antibiotics.

According to the present invention, combination of the indole derivatives of formula (1) with :

- glucocorticosteroids, in particular inhaled glucocorticosteroids with reduced systemic side effects, including ciclesonide, prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate, or

- muscarinic M3 receptor antagonists or anticholinergic agents including in particular ipratropium salts, namely bromide, tiotropium salts, namely bromide, oxitropium salts, namely bromide, perenzepine, and telenzepine,

are preferred.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment. The description, which follows, concerns the therapeutic applications to which the indole derivatives of formula (1) may be put.

The indole derivatives of formula (1) have the ability to interact with the β2 receptor and thereby have a wide range of therapeutic applications, as described further below, because of the essential role which the β2 receptor plays in the physiology of all mammals.

Therefore, a further aspect of the present invention relates to the indole derivatives of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of diseases, disorders, and conditions in which the β2 receptor is involved. More specifically, the present

invention also concerns the indole derivatives of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of diseases, disorders, and conditions selected from the group consisting of :

- asthma of whatever type, etiology, or pathogenesis, in particular asthma that is a member selected from the group consisting of atopic asthma, non-atopic asthma, allergic asthma, atopic bronchial IgE-mediated asthma, bronchial asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause, non-atopic asthma, bronchitic asthma, emphysematous asthma, exercise-induced asthma, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma, wheezy infant syndrome and bronchiolytis,

- chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction, and emphysema,

- obstructive or inflammatory airways diseases of whatever type, etiology, or pathogenesis, in particular an obstructive or inflammatory airways disease that is a member selected from the group consisting of chronic eosinophilic pneumonia, chronic obstructive pulmonary disease (COPD), COPD that includes chronic bronchitis, pulmonary emphysema or dyspnea associated or not associated with COPD, COPD that is characterized by irreversible, progressive airways obstruction, adult respiratory distress syndrome (ARDS), exacerbation of airways hyper-reactivity consequent to other drug therapy and airways disease that is associated with pulmonary hypertension,

- pneumoconiosis of whatever type, etiology, or pathogenesis, in particular pneumoconiosis that is a member selected from the group consisting of aluminosis or bauxite workers' disease, anthracosis or miners' asthma,

asbestosis or steam-fitters' asthma, chalicosis or flint disease, ptilosis caused by inhaling the dust from ostrich feathers, siderosis caused by the inhalation of iron particles, silicosis or grinders' disease, byssinosis or cotton-dust asthma and talc pneumoconiosis;

- bronchitis of whatever type, etiology, or pathogenesis, in particular bronchitis that is a member selected from the group consisting of acute bronchitis, acute laryngotracheal bronchitis, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, dry bronchitis, infectious asthmatic bronchitis, productive bronchitis, staphylococcus or streptococcal bronchitis and vesicular bronchitis,

- bronchiectasis of whatever type, etiology, or pathogenesis, in particular bronchiectasis that is a member selected from the group consisting of cylindric bronchiectasis, sacculated bronchiectasis, fusiform bronchiectasis, capillary bronchiectasis, cystic bronchiectasis, dry bronchiectasis and follicular bronchiectasis,

- central nervous system disorders of whatever type, etiology, or pathogenesis, in particular a central nervous system disorder that is a member selected from the group consisting of depression, Alzheimers disease, Parkinson's disease, learning and memory impairment, tardive dyskinesia, drug dependence, arteriosclerotic dementia and dementias that accompany Huntington's chorea, Wilson's disease, paralysis agitans, and thalamic atrophies,

- premature labor, and

- other type of diseases and conditions such as congestive heart failure, depression, inflammatory and allergic skin diseases, psoriasis, proliferative skin diseases, glaucoma and conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

A still further aspect of the present invention also relates to the use of the indole derivatives of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug having a β2 agonist activity. In particular, the present inventions concerns the use of the indole derivatives of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug for the treatment of β2-mediated diseases and/or conditions, in particular the diseases and/or conditions listed above.

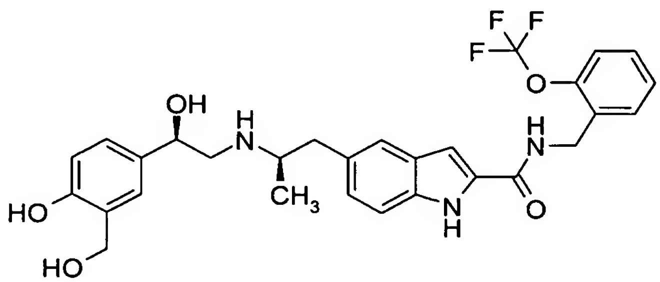
As a consequence, the present invention provides a particularly interesting method of treatment of a mammal, including a human being, including treating said mammal with an effective amount of an indole derivative of formula (1), or a pharmaceutically acceptable salt, derived form or composition thereof. More precisely, the present invention provides a particularly interesting method of treatment of a mammal, including a human being, to treat a β2-mediated diseases and/or conditions, in particular the diseases and/or conditions listed above, including treating said mammal with an effective amount of an indole derivative of formula (1), its pharmaceutically acceptable salts and/or derived forms.

The following examples illustrate the preparation of the indole derivatives of the formula (1) :

<u>Abbreviations:</u>

DMF	*N,N*-dimethylformamide
HOBt	1-hydroxybenzotriazole
WSCDI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
MeOH	methanol
THF	tetrahydrofuran
DIPEA	diisopropylethylamine
EtOH	ethanol
Et_2O	diethylether

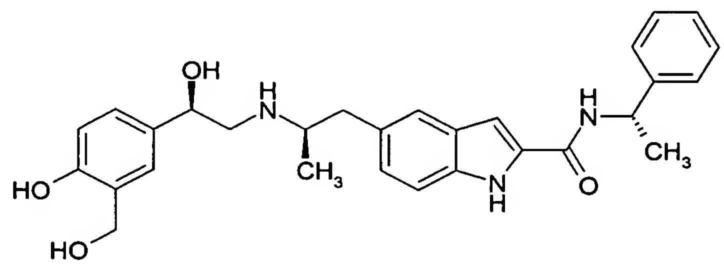
Example 1 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-trifluoromethoxybenzyl)-1H-indole-2-carboxamide



The acid from Preparation **6** (145 m g, 292 μmol) in DMF (1 ml) was treated with 2-trifluoromethoxybenzylamine (57 mg, 301 μmol), pyridine (26 mg, 325 μmol), HOBt (43 mg, 320 μmol) in DMF (1ml) and WSCDI (62 mg, 322 μmol) in DMF (1 ml) and the mixture shaken overnight. The solvent was removed *in vacuo* and replaced with CH_2Cl_2 (2ml) and water (0.5 ml). The organic phase was separated using a PTFE frit cartridge and the solvent removed *in vacuo*. Ammonium fluoride (108 mg, 292 μmol) in MeOH (1.9 ml) and water (1.1 ml) was added to the crude material and the mixture shaken at 40 °C overnight. The solvent was removed *in vacuo* and the crude material taken up in DMSO (1 ml) and filtered before being purified by reverse phase HPLC.

^{1}H NMR (400MHz, CD_3OD): δ 7.52-7.44 (3H, m), 7.40-7.31 (4H, m), 7.13 (3H, m), 6.77 (1H, d), 4.89 (1H, under solvent peak), 4.68 (2H, s), 4.65 (2H, s), 3.60 (1H, m), 3.28-3.138 (3H, m), 2.86 (1H, m), 1.28 (3H, d).
HRMS (ESI) : m/z $[M+H]^+$ found 558.2188; requires 558.2217.

Example 2 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-[(1*S*)-1-phenylethyl]-1H-indole-2-carboxamide

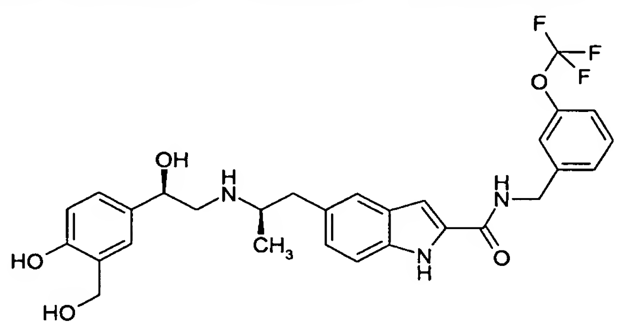


Prepared using the acid from Preparation **6** and the method described for Example **1**.

^{1}H NMR (400MHz, CD_3OD): contains ~ 23 % of the benzylamine δ 7.52 (1H, s), 7.42 (3H, t), 7.34-7.29 (4H, m), 7.24 (1H, m), 7.13 (2H, t), 6.77 (1H, d), 5.26 (1H, q), 4.88 (1H, under solvent peak), 4.65 (2H, s), 3.59 (1H, m), 3.27-3.12 (3H, m), 2.86 (1H, m), 1.58 (3H, d), 1.27 (3H, d).

HRMS (ESI) : m/z $[M+H]^+$ found 488.2528; requires 488.2551.

Example 3 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-(3-trifluoromethoxyphenylethyl)-1H-indole-2-carboxamide

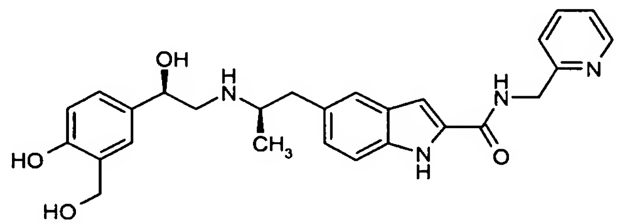


Prepared using the acid from Preparation **6** and the method described for Example **1**.

^{1}H NMR (400MHz, CD_3OD): δ 7.52 (1H, s), 7.46-.7.41 (2H, m), 7.36 (2H, m), 7.28 (1H, s), 7.15 (3H, m), 7.09 (1H, s), 6.78 (1H, d), 4.88 (1H, under solvent peak), 4.65 (2H, s), 4.62 (2H, s), 3.63-3.54 (1H, m), 3.28-3.13 (3H, m), 2.85 (1H, m), 1.27 (3H, d).

HRMS (ESI) : m/z $[M+H]^+$ found 558.2189; requires 558.2217.

Example 4 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-(pyridin-2-ylmethyl)-1H-indole-2-carboxamide

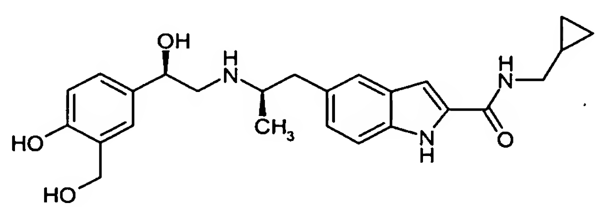


Prepared using the acid from Preparation **6** and the method described for Example **1**.

^{1}H NMR (400MHz, CD_3OD): δ 8.50 (1H, d), 7.80 (1H, m), 7.48 (1H, d), 7.36-7.29 (3H, m), 7.16 (1H, m), 7.06 (1H, s), 7.02-6.94 (2H, m), 6.59 (1H, d), 4.71 (2H, s), 4.60 (1H, m), 4.56 (2H, s), 2.79-2.68 (3H, m), 3.02 -2.91 (2H, m), 1.12 (3H, d).

HRMS (ESI) : m/z $[M+H]^+$ found 475.2324; requires 475.2347.

Example 5 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-(cyclopropylmethyl)-1H-indole-2-carboxamide

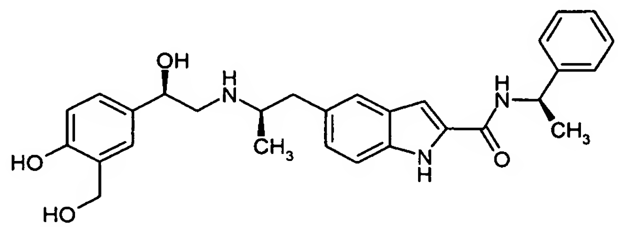


Prepared using the acid from Preparation **6** and the method described for Example **1**.

^{1}H NMR (400MHz, CD_3OD): δ 7.51 (1H, s), 7.43 (1H, d), 7.34 (1H, s), 7.13 (2H, m), 7.06 (1H, s), 6.77 (1H, d), 4.89 (1H, under solvent peak), 4.65 (2H, s), 3.62-3.55 (1H, m), 3.25-3.13 (5H, m), 2.85 (1H, m), 1.26 (3H, d), 1.10 (1H, m), 0.53 (2H, m), 0.30 (2H, m).

HRMS (ESI) : m/z $[M+H]^+$ found 438.2327; requires 438.2394.

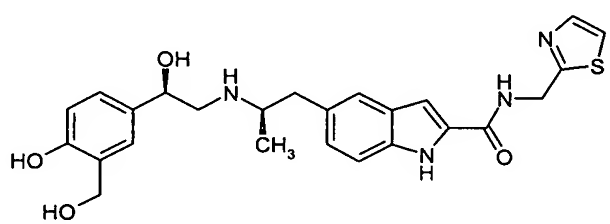
Example 6 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-[*(1R)*-1-phenylethyl]-1H-indole-2-carboxamide



A solution of Preparation **5** (240 mg, 399 μmol) in a mixture of methanol (14 ml) and water (8 ml) was treated with ammonium fluoride (148 mg, 3.99 mmol) and the resulting suspension heated at 40°C overnight. The solvent was removed in vacuo and the residue purified by flash chromatography [5 (+0.5 % NH_3) -10 % (+1.5% NH_3) MeOH in CH_2Cl_2] to give a white solid (82 mg).

^{1}H NMR (400MHz, CD_3OD): δ 7.42 (2H, m), 7.33 (4H, m), 7.23 (1H, t), 7.17 (1H, s), 7.09 (1H, s), 7.00-6.94 (2H, m), 6.59 (1H, d), 5.25 (1H, q), 4.58 (1H, m), 4.55 (2H, s), 2.99-2.89 (2H, m), 2.77-2.67 (3H, m), 1.59 (3H, d), 1.10 (3H, d).
LRMS (APCI) : m/z $[M+H]^+$ 488 $[M+H]^+$.

Example 7 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-(thiazol-2-ylmethyl)-1H-indole-2-carboxamide

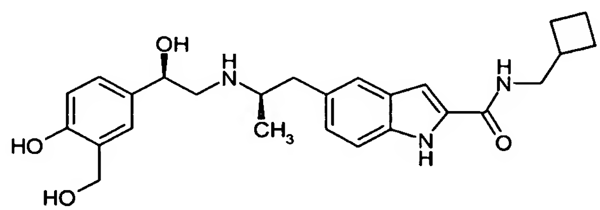


Prepared using the amide from Preparation **4** and the method described for Example **6**.

^1H NMR (400MHz, CD_3OD): δ 7.72 (1H, d), 7.51 (1H, d), 7.36 (2H, m), 7.20 (1H, s), 6.98-7.05 (3H, m), 6.63 (1H, d), 4.88 (2H, s), 4.64 (1H, m), 4.57 (2H, s), 3.06-3.11 (1H, m), 2.95 (1H, m), 2.69-2.87 (3H, m), 1.13 (3H, d).

HRMS (ESI) : m/z $[M+H]^+$ found 481.1901; requires 481.1911.

Example 8 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-(cyclobutylmethyl)-1H-indole-2-carboxamide

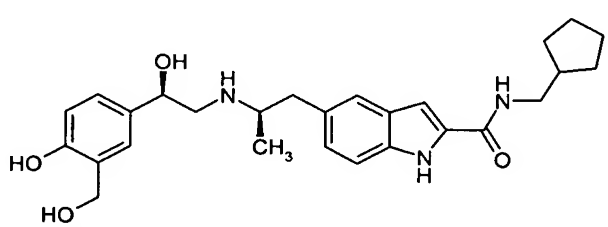


Prepared using the amide from Preparation **1** and the method described for Example **6**.

^1H NMR (400MHz, CD_3OD): δ 7.32 (2H, d), 7.18 (1H, s), 6.98 (3H, m), 6.60 (1H, d), 4.61 (1H, m), 4.56 (2H, s), 3.42 (2H, d), 3.02-2.89 (2H, m), 2.80-2.61 (4H, m), 2.15-2.07 (2H, m), 1.97-1.77 (4H, m), 1.11 (3H, d).

LRMS (ESI) : m/z $[M+H]^+$ 452.

Example 9 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-(cyclopentylmethyl)-1H-indole-2-carboxamide

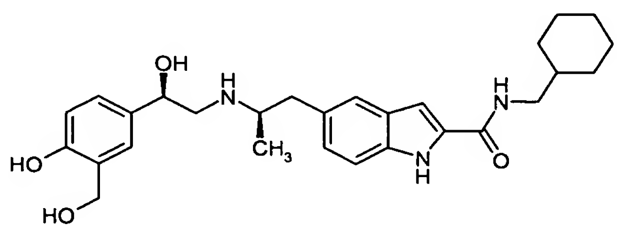


Prepared using the amide from Preparation **2** and the method described for Example **6**.

^1H NMR (400MHz, CD_3OD): δ 7.33 (2H, d), 7.19 (1H, s), 6.99 (3H, m), 6.62 (1H, d), 4.67-4.59 (1H, m), 4.57 (2H, s), 3.33 (2H, under solvent peak), 3.05 (1H, m),

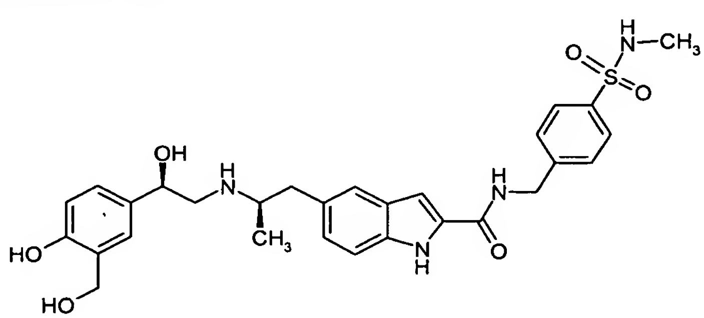
2.95 (1H, m), 2.85-2.68 (3H, m), 2.28-2.20 (1H, m), 1.85-1.77 (2H, m), 1.70-1.58 (4H, m), 1.37-1.28 (2H, m), 1.13 (3H, d).
HRMS (ESI) : m/z $[M+H]^+$ found 466.2694; requires 466.2707.

Example 10 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-(cyclohexylmethyl)-1H-indole-2-carboxamide



Prepared using the amide from Preparation **3** and the method described for Example **6**.
^{1}H NMR (400MHz, CD_3OD): δ 7.32 (2H, d), 7.12 (1H, s), 6.97 (3H, m), 6.60 (1H, d), 4.60 (1H, m), 4.56 (2H, s), 3.23 (2H, d), 3.07 -2.89 (2H, m), 2.79-2.63 (3H, m), 1.84-1.59 (6H, m), 1.34-1.18 (3H, m), 1.11 (3H, d), 1.08-0.97 (2H, m).
HRMS (ESI) : m/z $[M+H]^+$ found 480.2839; requires 480.2864.

Example 11 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-(4-methylsulfamoylbenzyl)-1H-indole-2-carboxamide



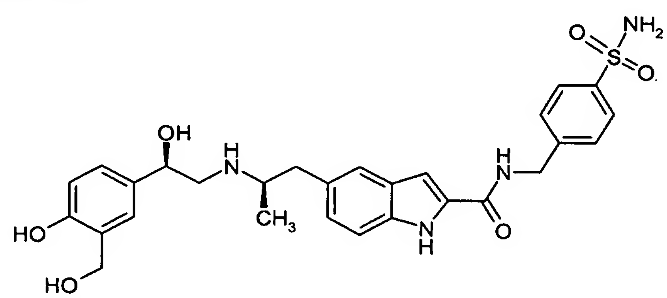
Preparation **6** (100 mg, 201 μmol), WSCDI (42 mg, 221 μmol), HOBt (30 mg, 221 μmol), pyridine (17 mg, 221 μmol) and 4-aminomethyl-*N*-methylbenzenesulfonamide (40 mg, 201 μmol) were stirred in DMF (5 ml) overnight. The solvent was removed and the product taken up in CH_2Cl_2 and

washed with water. The solvent was removed and the crude material taken up in MeOH (5.7 ml) and water (10 ml) and treated with ammonium fluoride (43 mg, 115 μmol) and stirred at 40 °C overnight. The solvent was removed and the crude material purified twice by chromatography (10-20 % MeOH in CH_2Cl_2 + 1 % ammonia) (18 mg).

^1H NMR (400MHz, CD_3OD): δ 7.79 (2H, d) 7.58 (3H, d), 7.43 (1H, d), 7.45 (1H, s), 7.15 (3H, t), 6.78 (1H, d), 4.62 (5H, d), 3.59 (1H, m), 3.19 (1H, m), 3.18 (2H, m), 2.85 (1H, t), 2.50 (3H, s), 1.25 (3H, d).

LRMS (ESI) : m/z $[M+H]^+$ 567.

<u>Example 12 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-(4-sulfamoylbenzyl)-1H-indole-2-carboxamide</u>

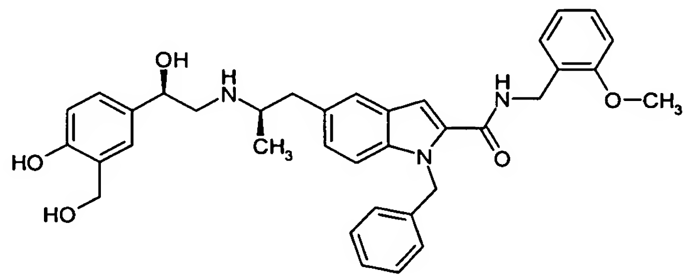


Prepared using the acid from Preparation **6** and the method described for Example **11**.

^1H NMR (400MHz, CD_3OD): δ 7.82 (2H, d), 7.50 (3H, d), 7.42 (1H, d), 7.30 (1H, s), 7.12 (2H, d), 7.09 (1H, s), 6.78 (1H, d), 4.62 (5H, d), 3.60 (1H, m), 3.22 (1H, m), 3.18 (2H, m), 2.82 (1H, m), 1.22 (3H, d).

LRMS (ESI) : m/z $[M+H]^+$ 553.

Example 13 : 1-Benzyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl) ethyl}amino)propyl}-*N*-(2-methoxybenzyl)-1H-indole-2-carboxamide

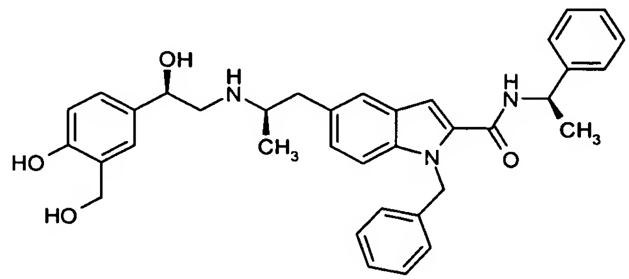


A solution of Preparation **31** (100 mg, 170 μmol), WSCDI (42 mg, 219 μmol), HOBt (34 mg, 255 μmol) and pyridine (33 mg, 340 μmol) in DMF (2 ml) was treated with 2-methoxybenzylamine (23 mg, 170 μmol) and the mixture stirred at RT under a nitrogen atmosphere for 18 hours. The solvent was removed and residue partitioned between CH_2Cl_2 (6 ml) and water (6 ml). The organic phase was reduced in vacuo and the crude material was taken up in MeOH (8 ml) and treated with ammonium fluoride (72 mg, 1.95 mmol) in water (4 ml) and stirred at 40 °C overnight. The solvent was removed and the product purified by chromatography (2% MeOH in CH_2Cl_2 + 0.2 % ammonia) (20 mg).

^{1}H NMR (400MHz, CD_3OD): δ 7.33 (1H, s), 7.28-7.11 (7H, m), 7.01-6.92 (6H, m), 6.83 (1H, t), 6.60 (1H, d), 5.77 (2H, s), 4.61-4.57 (1H, m), 4.55 (2H, s), 5.42 (2H, s), 3.83 (3H, s), 2.98-2.88 (2H, m), 2.76-2.65 (3H, m), 1.09 (3H, d).

LRMS (ESI) : m/z $[M+H]^+$ 594.

Example 14 : 1-Benzyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl) ethyl}amino)propyl}-*N*-[*(1R)*-1-phenylethyl]-1H-indole-2-carboxamide

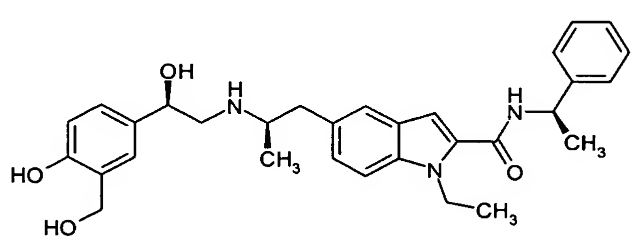


Prepared using the acid from Preparation **31** and the method described for Example **13**.

^{1}H NMR (400MHz, CD_3OD): δ 7.39-6.99 (16H, m), 6.65 (1H, d), 5.75 (2H, s), 5.21 (1H, q), 4.66-4.60 (3H, m), 2.93-3.02 (2H, m), 2.80-2.70 (3H, m), 1.57 (3H, d), 1.14 (3H, d) .

LRMS (ESI) : m/z $[M+H]^+$ 578.

Example 15 : 1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl) ethyl}amino)propyl}-*N*-[*(1R)*-2-phenylethyl)-1H-indole-2-carboxamide



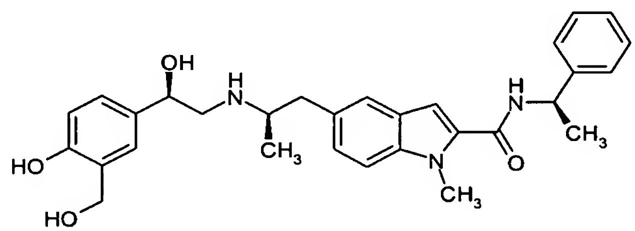
Prepared using the acid from Preparation **26** and the method described for Example **13**.

^{1}H NMR (400MHz, CD_3OD): δ 7.45 (2H, m), 7.39-7.32 (4H, m), 7.26 (1H, m), 7.21 (1H, bs), 7.06 -6.98 (3H, m), 6.64 (1H, d), 5.26 (1H, q), 4.63 (1H, m), 4.57

(2H, m), 4.52 (2H, q), 3.01-2.93 (2H, m), 2.75-2.68 (3H, m), 1.61 (3H, d), 1.32 (3H, t), 1.14 (3H, d).

LRMS (ESI) : m/z $[M+H]^+$ 516.

Example 16 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)propyl}-*N*-[(*1R*)-1-phenylethyl)-1-methyl-1H-indole-2-carboxamide

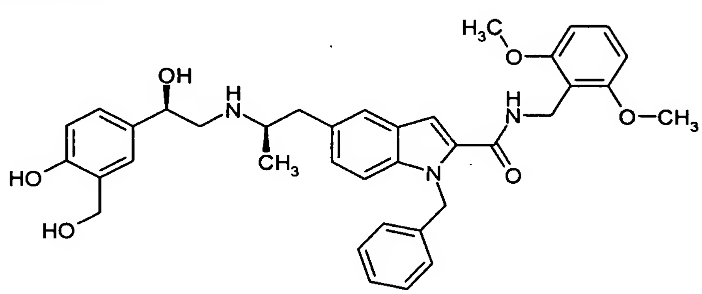


Prepared using the acid from Preparation **21** and the method described for Example **13**.

^{1}H NMR (400MHz, CD_3OD): δ 7.43 (2H, d), 7.33 (2H, t), 7.27-7.23 (3H, m), 7.13 (1H, bs), 7.00-6.89 (3H, m), 6.54 (1H, d), 5.23 (1H, q), 4.57-4.54 (1H, m), 4.54-4.46 (2H, m), 3.91 (3H, m), 2.95-2.87 (2H, m), 2.74-2.59 (3H, m), 1.58 (3H, d), 1.10 (3H, d).

LRMS (ESI) : m/z $[M+H]^+$ 502.

Example 17 : 1-Benzyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl) ethyl}amino)propyl}-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide

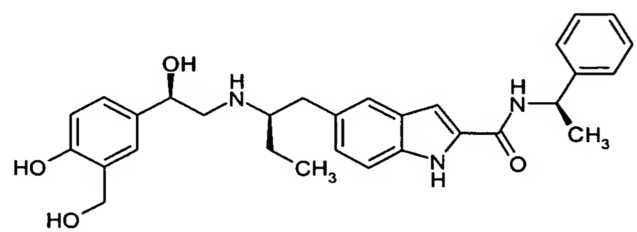


Prepared using the acid from Preparation **31** and the method described for Example **13**.

[1]H NMR (400MHz, CD_3OD): δ 7.33-7.89 (12H, m), 6.70 (2H, s), 6.62 (1H, d), 5.81 (2H, s), 4.66-4.58 (5H, m), 3.86 (6H, s), 2.99-2.90 (2H, m), 2.76-2.67 (3H, m), 1.13 (3H, d).

LRMS (ESI) : m/z $[M+H]^+$ 624.

Example 18 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)butyl}-*N*-[(*1R*)-1-phenylethyl]-1H-indole-2-carboxamide

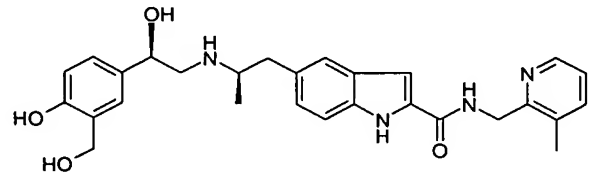


A solution of Preparation **39** (153 mg, 220 μmol) in ethanol (10 ml) was treated with ammonium formate (70 mg, 1.1 mmol) and palladium hydroxide on carbon (20 %, 10 mg) and heated to reflux for 2 h. Ammonium fluoride (40 mg, 1.1 mmol) in water (1 ml) was then added and the resulting mixture stirred at 40 °C for 24 h. The solvents were then removed and the crude material taken up in ethyl acetate, washed with water (containing 1 % 0.88 ammonia) and dried (Na_2SO_4). The product was purified by chromatography (2-5 % MeOH in CH_2Cl_2 and 0.3 % NH_3) to yield a yellow semi-solid. This was taken up in THF (3 ml) and water (0.5 ml) and treated with LiOH (1N, 100 μl) and stood at RT overnight. The solvents were removed and the product purified by chromatography (5 % MeOH in CH_2Cl_2 + 0.3 % MeOH) (60 mg).

[1]H NMR (400MHz, CD_3OD): δ 7.43-7.41 (2H, m), 7.34-7.27 (4H, m), 7.22 (1H, t), 7.15 (1H, m), 7.09 (1H, s), 7.00-6.90 (2H, d), 6.57 (1H, d), 5.26 (1H, q), 4.55 (3H, m, s), 2.87-2.60 (5H, m), 1.58 (3H, d), 1.55 (1H, m), 1.44 (1H, m), 0.96 (3H, t).

LRMS (ESI) : m/z $[M+H]^+$ 502.

Example 19 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl} amino)butyl}-*N*-[3-methyl-pyridin-2-ylmethyl]-1H-indole-2-carboxamide



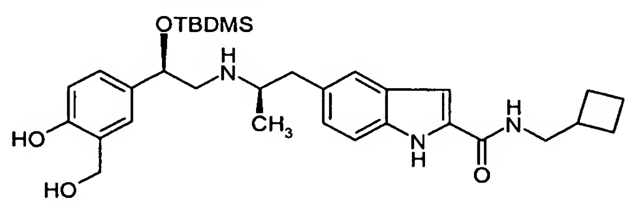
Prepared using the acid from Preparation **41** and the method described for Preparation **6**.

^{1}H NMR (400MHz, CD_3OD): δ 8.40 (1H, d), 7.65 (1H, d), 6.90-7.35 (7H, m), 6.60 (1H, d), 4.70 (2H, s), 4.60 (1H, m), 4.50 (2H, s), 2.60-3.00 (5H, m), 2.40 (3H, s), 1.05 (3H, d).

HRMS : $C_{28}H_{32}N_4O_4Si$ requires : 489.2503 found 489.2492 $[M+H]^+$.

The following Preparations describe the preparation of certain intermediates used in the preceding Examples.

Preparation 1 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxy methyl)phenyl]ethyl}amino)propyl]-*N*-[cyclobutylmethyl]-1*H*-indole-2-carboxamide



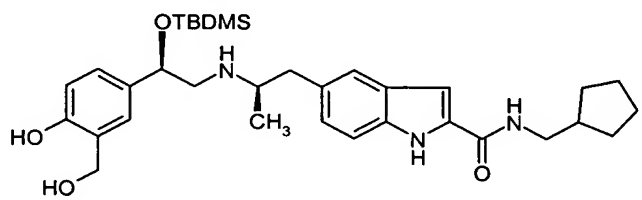
A solution of Preparation **6** (150 mg, 300 μmol), WSCDI (63 mg, 330 μmol), HOBt (45 mg, 330 μmol) and pyridine (54 mg, 661 μmol) in DMF (2 ml) was treated with Preparation 40 (40 mg, 330 μmol) and the mixture stirred at RT under a nitrogen atmosphere for 18 hours. The solvent was removed and the crude material taken up in CH_2Cl_2:MeOH (9:1) (10 ml) and washed with sat. ammonium chloride solution (2x 5 ml). The precipitate was redissolved in CH_2Cl_2:MeOH (9:1) (10 ml) and the combined organics dried (Na_2SO_4). After

removal of the solvent the material was triturated with EtOH and Et_2O and the solid filtered off. The filtrate left a light brown coloured foam (144 mg).

^1H NMR (400MHz, CD_3OD): δ 7.50 (2H, m), 7.32 (1H, s), 7.10 (3H, m), 6.80 (1H, d), 5.03 (1H, m), 4.65 (2H, dd), 3.40 (2H, m), 3.05-3.12 (3H, m), 2.95 (1H, m), 2.65 (2H, m), 2.10 (2H, m), 1.90 (2H, m), 1.80 (2H, m), 1.33 (3H, d), 0.78 (9H, s), 0.00 (3H, s), -0.20 (3H, s).

LRMS (electrospray) : m/z $[M+H]^+$ 566.

Preparation 2 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxy methyl)phenyl]ethyl}amino)propyl]-*N*-(cyclopentylmethyl)-1*H*-indole-2-carboxamide

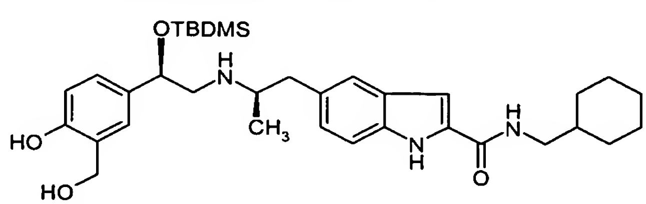


Prepared using the acid from Preparation **6** and the method described for Preparation **1**.

^1H NMR (400MHz, CD_3OD): δ 7.48 (2H, m), 7.30 (1H, s), 7.10 (3H, m), 6.78 (1H, d), 5.01 (1H, m), 4.70-4.61 (2H, m), 3.60 (1H, m), 3.36 (2H, under solvent peak), 3.18-3.08 (3H, m), 2.94 (1H, m), 2.24 (1H, m), 1.84-1.76 (2H, m), 1.68-1.58 (4H, m), 1.36-1.29 (5H, m), 0.76 (9H, s), 0.00 (3H, s), -0.19 (3H, s).

LRMS (electrospray) : m/z $[M+H]^+$ 580.

Preparation 3 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxy methyl)phenyl]ethyl}amino)propyl]-*N*-(cyclohexylmethyl)-1*H*-indole-2-carboxamide

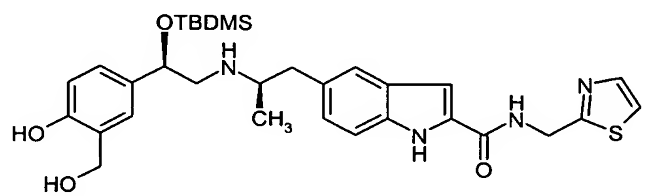


Prepared using the acid from Preparation **6** and the method described for Preparation **1**.

^{1}H NMR (400MHz, CD_3OD): δ 7.42 (2H, m), 7.24 (1H, s), 7.04 (3H, m), 6.71 (1H, d), 4.88 (1H, under solvent peak), 4.63 (2H, m), 3.35 (1H, under solvent peak), 3.23 (2H, d), 3.15 (1H, m), 2.96-2.82 (3H, m), 1.83-1.60 (6H, m), 1.33-1.17 (3H, m), 1.22 (3H, d), 0.98 (2H, q), 0.74 (9H, s), -0.05 (3H, s), -0.23 (3H, s).

LRMS (electrospray) : m/z $[M+H]^+$ 594.

Preparation 4 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxy methyl)phenyl]ethyl}amino)propyl]-*N*-(thiazol-2-ylmethyl)-1*H*-indole-2-carboxamide

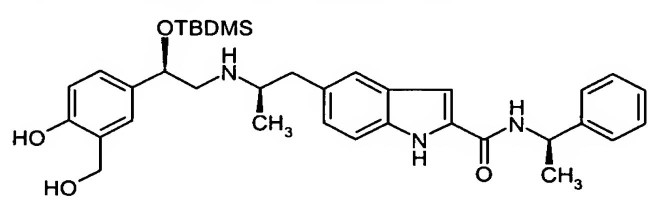


Prepared using the acid from Preparation **6** and the method described for Preparation **1**.

^{1}H NMR (400MHz, CD_3OD): δ 7.71 (1H, d), 7.50 (1H, d), 7.34 (2H, m), 7.16 (1H, s), 7.06 (1H, s), 7.01 (1H, d), 6.93 (1H, d), 6.61 (1H, d), 4.89 (2H, s), 4.68 (1H, m), 4.54-4.62 (2H, m), 2.99 (1H, m), 2.90 (1H, m), 2.71 (2H, d), 2.64 (1H, m), 1.09 (3H, d), 0.71 (9H, s), -0.09 (3H, s), -0.26 (3H, s).

LRMS (APCI) : m/z $[M+H]^+$ 595.

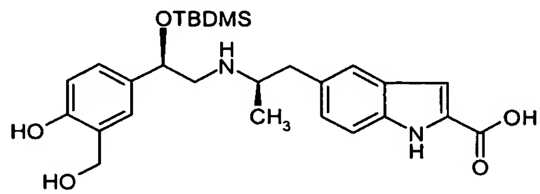
Preparation 5 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxy methyl)phenyl]ethyl}amino)propyl]-*N*-[(1*R*)-1phenylethylamine)-1*H*-indole-2-carboxamide



Prepared using the acid from Preparation **6** and the method described for Preparation **1**.

^{1}H NMR (400MHz, CD_3OD) : crude material
LRMS (APCI) : m/z $[M]^+$ 602.

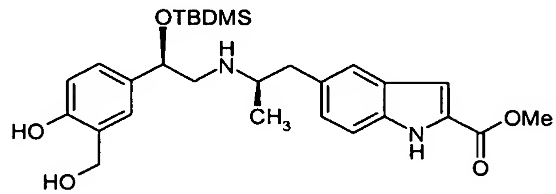
Preparation 6 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxy methyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylic acid



A solution of Preparation **7** (0.30 g, 0.59 mmol) in 1,4-dioxane (10 ml) was treated with a solution of sodium hydroxide (59 mg, 1.46 mmol) in water (1 ml) and the resulting mixture left to stir at room temperature for 30 minutes. After this time the reaction mixture was heated to 90°C for 30 minutes and then cooled to room temperature. The solvent was removed in vacuo and the residue re-dissolved in water (20 ml) and pH adjusted to 7 by addition of 2N hydrochloric acid. The solid that formed was filtered off, solubilised in a mixture of dichloromethane and methanol (20 ml 90:10 by volume), dried (magnesium sulphate) and the solvent removed in vacuo to give the title compound as a pale orange foam.

^{1}H NMR (400MHz, CD_3OD): δ = 7.47-7.42 (2H, m), 7.27 (1H, s), 7.11-7.03 (3H, m), 6.76-6.74 (1H, d), 4.99-4.97 (1H, m), 4.67-4.58 (2H, m); 3.60-3.55 (1H, m), 3.28-3.26 (1H, m), 3.16-3.12 (1H, m), 3.09-3.04 (1H, m), 2.94-2.88 (1H, m), 1.28-1.26 (3H, d), 0.74 (9H, s), -0.03 (3H, s), -0.22 (3H, s).
LRMS (electrospray) : m/z $[M+H]^+$, 499.

Preparation 7 : Methyl 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylate



A suspension of Preparation **8** (0.38 g, 0.63 mmol) and 10% palladium on carbon (78 mg) in ethanol (20 ml) was stirred under an atmosphere of hydrogen (60psi) at room temperature for 16 hours. The catalyst was filtered off through arbocel and the solvent removed in vacuo to give the title compound as a pale pink foam (316 mg), which was used without further purification.

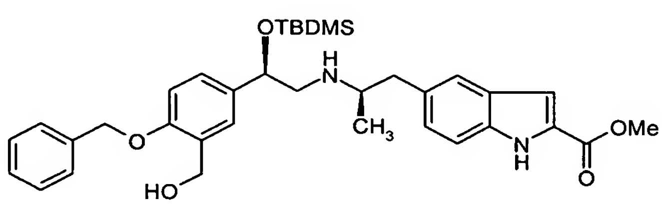
^{1}H NMR (400MHz, CD_3OD): δ = 7.36-7.32 (2H, m), 7.15 (1H, bs), 7.09 (1H, bs), 7.05-7.04 (1H, m), 6.95-6.93 (1H, m), 6.62 (1H, d), 4.69-4.66 (1H, m), 4.57 (2H, s), 3.92 (3H, s), 2.98-2.85 (2H, m), 2.70 (2H, d), 2.63-2.59 (1H, m), 1.08 (3H, d), 0.71 (9H, s), -0.09 (3H, s), -0.26 (3H, s).

LRMS (electrospray) : m/z $[M+H]^+$513, $[M+Na]^+$ 535.

Analysis : Found C 64.89; H 7.93; N 5.08; $C_{28}H_{40}N_2O_5Si$. $0.25H_2O$ requires C 65.02; H 7.89; N 5.42

Optical Rotation $[\alpha]_D^{25}$ = -84.02° 0.4mg/ml MeOH 635nm

Preparation 8 : Methyl 5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]propyl}-1*H*-indole-2-carboxylate



Preparation **9** (4.55 g, 19.6 mmol), Preparation **15** (8.55 g, 19.6 mmol) and diisopropylethylamine (2.53 g, 19.6 mmol) were stirred and heated to 100 °C overnight. Ethyl acetate (300 ml) was added and the organic washed with water (2x 500 ml). The aqueous phases were washed with ethyl acetate (200

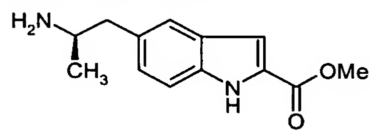
ml) and the combined organics washed with brine (500 ml) and dried (Na_2SO_4). The crude material was purified by chromatography (0-3 % MeOH in CH_2Cl_2 with 0.5 % NH_3) the title compound as a pale yellow oil (5.72 g).

^1H NMR (400MHz, CD_3OD): δ = 7.44-7.27 (8H, m), 7.08-7.04 (2H, m), 6.96-6.93 (1H, m), 6.67 (1H, d), 4.98 (2H, s), 4.72-4.67 (1H, m), 4.60 (2H, s), 3.82 (3H, s), 2.99-2.89 (2H, m), 2.77-2.72 (1H, m), 2.65-2.59 (2H, m), 1.11 (3H, d), 0.74 (9H, s), -0.07 (3H, s), -0.24 (3H, s).

LRMS (electrospray) : m/z $[M+H]^+$603, $[M+Na]^+$ 625.

Analysis : Found C 69.26; H 7.72; N 4.61; $C_{35}H_{46}N_2O_5Si$. $0.2H_2O$ requires C 69.32; H 7.71; N 4.62

<u>Preparation 9 : Methyl 5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate</u>



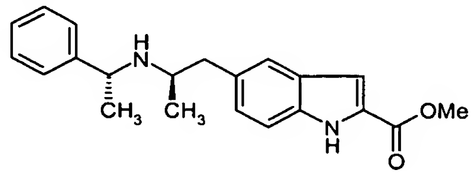
A solution of Preparation **10** (9.34 g, 25.0 mmol) in ethanol (125 ml) was treated with ammonium formate (7.90 g, 125 mmol) and palladium hydroxide on carbon (2.81 g, 20% b/w palladium). The resulting suspension was purged with nitrogen and then heated to reflux for an hour. The reaction mixture was cooled to room temperature and filtered through arbocel to remove catalyst residues. The filtrate was reduced in vacuo and the residue was partitioned between 0.88 ammonia (100 ml) and dichloromethane (100 ml). The organic phase was separated and the aqueous extracted with more dichloromethane (100 ml). The combined organic extracts were dried (sodium sulphate) and the solvent removed in vacuo to give the title compound as a colourless oil (6.25 g, trace solvent remaining by ^1H NMR).

^1H NMR (400MHz, CD_3OD): δ = 7.44 (1H, bs), 7.36 (1H, d), 7.13 (1H, d), 7.11 (1H, s), 3.90 (3H, s), 3.17-3.07 (1H, m), 2.77-2.61 (2H, m), 1.10 (3H, d).

LRMS (electrospray) : m/z $[M+H]^+$ 233, $[M+Na]^+$ 255.

Optical Rotation $[\alpha]_D^{25}$ = -22.58° 6.76mg/ml MeOH 589nm

Preparation 10 : Methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-2-carboxylate hydrochloride

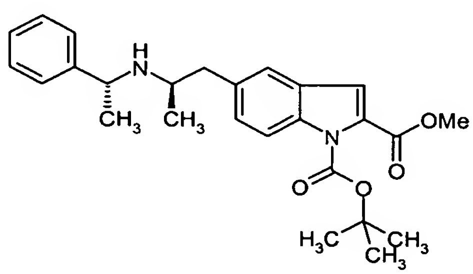


A solution of Preparation **11** (20.48 g, 46.9 mmol) was treated with 4M hydrogen chloride in methanol and the resulting solution left to stir at room temperature for 16 hours and then heated at 50°C for a further 2 hours. The solvent was removed in vacuo to give a solid which was crystallised from a mixture of methanol (125 ml) and diisopropylether (50 ml) to give the title compound as a colourless crystalline solid (9.34 g, d.e.>98% as determined by ^{1}H NMR).

^{1}H NMR (400MHz, CD_3OD): δ = 7.53-7.49 (5H, m), 7.40-7.38 (2H, m), 7.10, 1H, bs), 6.97 (1H, bd), 4.61 (1H, q), 3.91 (3H, s), 3.42-3.37 (1H, m), 3.26-3.19 (1H, m), 2.72-2.66 (1H, m), 1.69 (3H, d), 1.19 (3H, d).

LRMS (electrospray) : m/z $[M+H]^+$ 337.

Preparation 11 : 1-*tert*-butyl 2-methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino} propyl)-1*H*-indole-1,2-dicarboxylate



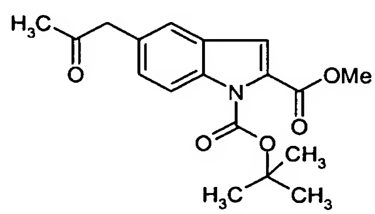
A solution of Preparation **12** (18.0 g, 54.32 mmol), (*R*)-α-methylbenzylamine (6.4 ml, 49.65 mmol), sodium triacetoxyborohydride (15.80 g, 74.55 mmol) and acetic acid (3.0 ml, 52.38 mmol) in dichloromethane (500 ml) was stirred at room temperature for 16 hours. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate (200 ml) and allowed to stir until effervescence ceased. The organic phase was separated and the aqueous

phase extracted with further dichloromethane (100 ml). The combined organic extracts were dried (magnesium sulphate) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (99:1:0.1 changing to 98:2:0.2, by volume) to give a 4:1 mixture of diastereomers (*R*,*R* major) as a pale yellow oil (20.48 g).

^{1}H NMR (400MHz, CD_3OD): δ = 7.97-7.92 (1H, m), 7.41-7.02 (8H, m), 4.04-3.99 (1H, m), 3.96-3.94 (3H, m), 3.15-3.10 (1H, m), 2.80-2.70 (1H, m), 2.53-2.48 (1H, m), 1.66 (9H, s), 1.39-1.31 (3H, 2d), 1.10-0.95 (3H, 2d).

LRMS (electrospray) : m/z $[M+H]^+$ 437.

<u>Preparation 12 : 1-*tert*-butyl 2-methyl 5-(2-oxopropyl)-1*H*-indole-1,2-dicarboxylate</u>

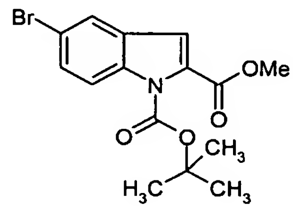


A solution of Preparation **13** (12.5 g, max 32.04 mmol), tributyltin methoxide (11.0 ml, 38.2 mmol), isoprenylacetate (5.3 ml, 48.1 mmol), palladium acetate (0.36 g, 5 mol%), tri-o-tolylphosphine (0.97 g, 10 mol%) in toluene (40 ml) was degassed and then heated at 100°C for 8 hours. The reaction mixture was diluted with ethyl acetate (50 ml), 4M potassium fluoride (aqueous, 100 ml) and left to stir at room temperature overnight. The resulting mixture was filtered through arbocel washing the precipitate thoroughly with ethyl acetate (100 ml) and the organic phase of the filtrate separated, dried (magnesium sulphate) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (95:5 changing to 90:10, by volume) to give the title compound (8.2 g) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.05 (1H, d), 7.44 (1H, s), 7.25 (1H, d), 7.05 (1H, s), 3.92 (3H, s), 3.78 (2H, s), 2.16 (3H, s), 1.61 (9H, s).

LRMS (electrospray) : m/z $[M-H]^-$ 330, $[M+Na]^+$ 354.

Preparation 13 : 1-*tert*-Butyl 2-methyl 5-bromo-1*H*-indole-1,2-dicarboxylate

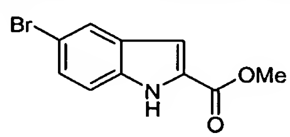


A solution of Preparation **14** (8.14 g, 32.04 mmol) in tetrahydrofuran (300 ml) was added to sodium hydride (1.35 g of a 40% dispersion in mineral oil, 33.7 mmol) at 0°C under nitrogen. The resulting mixture was left to stir until effervescence ceased (50 minutes). A solution of di-*tert*-butyldicarbonate in further tetrahydrofuran (30 ml) was added to the reaction and the resulting mixture stirred vigorously, warming gradually to room temperature overnight. The solvent was removed in vacuo and the residue partitioned between ethyl acetate (200 ml) and water (200 ml). The organic phase was separated and the aqueous extracted with more ethyl acetate (2-fold 200 ml). The combined organics were dried (magnesium sulphate) and the solvent removed in vacuo to give the title compound as a pale yellow oil (12.5 g – trace solvent remaining).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.98 (1H, d), 7.74 (1H, s), 7.50 (1H, dd), 7.00 (1H, s), 3.92 (3H, s), 1.61 (9H, s).

LRMS (electrospray) : m/z $[M+H]^+$ 352 / 354, $[M+Na]^+$ 376 / 378.

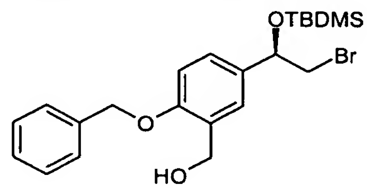
Preparation 14 : Methyl 5-bromo-1*H*-indole-2-carboxylate



A solution of 5-Bromo-1*H*-indole-2-carboxylic acid (commercial, 10.0 g, 41.6 mmol) in methanol (200 ml) was cooled to 0 °C and saturated with HCl (g). The resulting solution was allowed to warm gradually to room temperature overnight. The solvent was removed in vacuo and the residue treated with 0.88 ammonia (500 ml). The resulting solution was extracted with dichloromethane (3-fold 150 ml) and the combined organics dried (magnesium sulphate) and the solvent removed in vacuo to give the required product as a colourless oil (8.35 g).

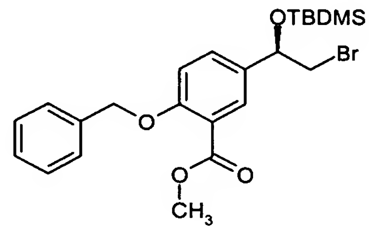
^1H NMR (400MHz, $CDCl_3$): δ = 8.96 (1H, bs), 7.83 (1H, s), 7.40 (1H, d), 7.30 (1H, d), 7.14 (1H, s), 3.95 (3H, s).
LRMS (electrospray) : m/z $[M-H]^-$ 252 / 254.

Preparation 15 : [2-(benzyloxy)-5-((1*R*)-2-bromo-1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl) phenyl]methanol



Borane methylsulfide complex (42.4 ml of ~10M solution, 424 mmol) was added drop wise to a solution of Preparation **16** (91.0 g) in tetrahydrofuran (1600 ml). The resulting mixture was then heated to reflux for 2 hours and then cooled to 0 °C before quenching with methanol (270 ml). The mixture was left to stir at room temperature for 16 hours and then the solvent removed in vacuo. The residue was partitioned between dichloromethane (500 ml) and water (500 ml). The aqueous phase was separated and extracted with more dichloromethane (500 ml) and the combined organic extracts washed with saturated aqueous sodium chloride (500 ml), dried (magnesium sulphate) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel eluting with cyclohexane:ethyl acetate (100:0 changing to 80:20, by volume) to give the title compound (68.7 g) as a colourless oil.
^1H NMR (400MHz, $CDCl_3$): δ = 7.42-7.36 (5H, m), 7.29-7.25 (3H, m), 6.94 (1H, d), 5.12 (2H, s), 4.84-4.81 (1H, m), 4.74 (2H, s), 3.48-3.40 (2H, m), 0.90 (9H, s), 0.11 (3H, s), -0.07 (3H, s).
LRMS (electrospray) : m/z $[M+Na]^+$ 473 / 475.

<u>Preparation 16 : Methyl 2-(benzyloxy)-5-((1*R*)-2-bromo-1-{[*tert*-butyl(dimethyl)silyl]oxy} ethyl)benzoate</u>

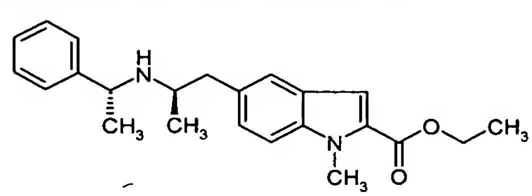


A solution of methyl 2-(benzyloxy)-5-[(1*R*)-2-bromo-1-hydroxyethyl]benzoate (71.05 g, 195 mmol), imidazole (18.52 g, 272 mmol), *tert*-butyldimethylsilyl chloride (32.23 g, 214 mmol) and 4-(dimethylamino)pyridine (0.44 g, 3.6 mmol) in DMF (270 ml) was left to stir at room temperature under a nitrogen atmosphere for a period of 24 hours. The solvent was removed in vacuo and the residue partitioned between ethyl acetate (500 ml) and water (500 ml). The organic phase was separated and washed with 2N hydrochloric acid (2-fold 500 ml), saturated aqueous sodium bicarbonate (2x 500 ml) saturated sodium chloride (500 ml), dried (magnesium sulphate) and the solvent removed in vacuo to give the title compound as a colourless oil (91.0 g).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.81 (1H, bs), 7.51-7.30 (6H, m), 7.01 (1H, d), 5.19 (2H, s), 4.85-4.82 (1H, m), 3.91 (3H, s), 3.48-3.39 (2H, m), 0.90 (9H, s), 0.11 (3H, s), -0.08 (3H, s).

LRMS (electrospray) : m/z $[M+Na]^+$ 501 / 503.

<u>Preparation 17 : Ethyl 1-methyl-5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino} propyl)-1*H*-indole-2-carboxylate hydrochloride</u>

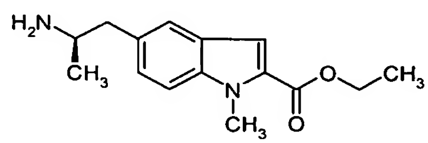


Prepared using the procedure of Preparation **11** giving the title compound as a a 4:1 mixture of diastereomers (R,R major). The crude material was treated

with excess HCl in MeOH and then crystallised from DIPE / MeOH to give the R,R isomer (d.e.>98% as determined by ^{1}H NMR).

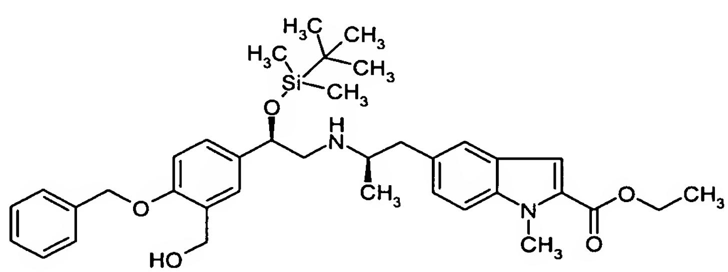
^{1}H NMR (400 MHz, CD_3OD) : δ 7.56-7.48 (5H, m), 7.43-7.40 (2H, m), 7.19 (1H, s), 7.04 (1H, d), 4.62 (1H, q), 4.35 (2H, q), 4.03 (3H, s), 3.45-3.40 (1H, m), 3.28-3.21 (1H, m), 2.74-2.69 (1H, m), 1.70 (3H, d), 1.39 (3H, t), 1.19 (3H, d).
LRMS (ESI) : m/z $[M+H]^+$ 635, $[M+Na]^+$ 387.

Preparation 18 : Ethyl 1-methyl-5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate



Prepared using the amine from Preparation **17** and the method described for Preparation **9**.
^{1}H NMR (400 MHz, CD_3OD) : δ 7.46-7.40 (2H, m), 7.22-7.19 (2H, m), 4.35 (2H, q), 4.04 (3H, s), 3.18-3.10 (1H, m), 2.77-2.65 (2H, m), 1.39 (3H, t), 1.10 (3H, d).
LRMS (ESI) : m/z $[M+H]^+$ 261, $[M+Na]^+$ 283.

Preparation 19 : Ethyl 1-methyl-5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl) phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino] propyl}-1*H*-indole-2-carboxylate

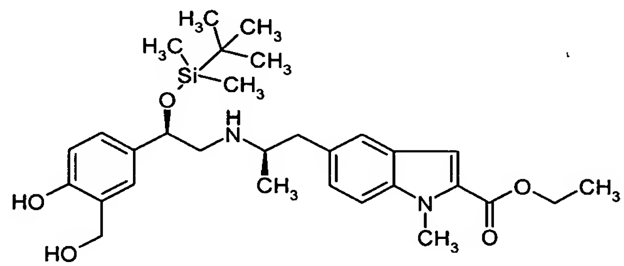


Prepared using the amine from Preparation **18**, and the bromide from Preparation **15** and the method described for Preparation **8**.
^{1}H NMR (400 MHz, CD_3OD) : δ 7.43-7.26 (8H, m), 7.18 (1H, bs), 7.10 (1H, d), 6.98 (1H, d), 6.72 (1H, d), 4.99 (2H, s), 4.71-4.68 (1H, m), 4.58 (2H, s), 4.29

(2H, q), 4.01 (3H, s), 2.98-2.90 (2H, m), 2.78-2.73 (1H, m), 2.65-2.58 (2H, m), 1.36 (3H, t), 1.11 (3H, d), 0.73 (9H, s), -0.07 (3H, s), -0.24 (3H, s).

LRMS (ESI) : m/z $[M+H]^+$ 631, $[M+Na]^+$ 653.

Preparation 20 : Ethyl 1-methyl-5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylate

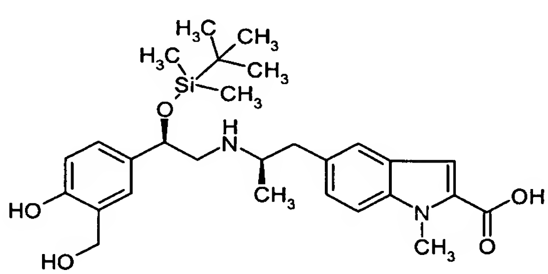


Prepared using the ester from Preparation **19** and the method described for Preparation **7**.

^{1}H NMR (400 MHz, CD_3OD) : δ 7.35-7.31 (2H, m), 7.18 (1H, s), 7.11-7.06 (2H, m), 6.92 (1H, d), 6.58 (1H, d), 4.66-4.63 (1H, m), 4.53 (2H, s), 4.37 (2H, q), 4.05 (3H, s), 2.96-2.87 (2H, m), 2.76-2.56 (3H, m), 1.40 (3H, t), 1.10 (3H, d), 0.72 (9H, s), -0.08 (3H, s), -0.26 (3H, s).

LRMS (ESI) : m/z $[M+H]^+$ 541, $[M+Na]^+$ 563.

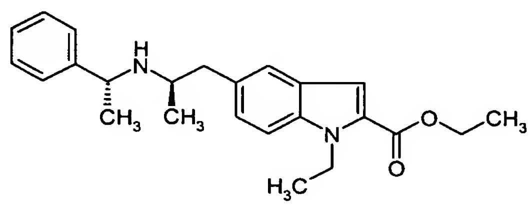
Preparation 21 : 1-Methyl-5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylic acid



Prepared using the ester from Preparation **20** and the method described for Preparation **6**.

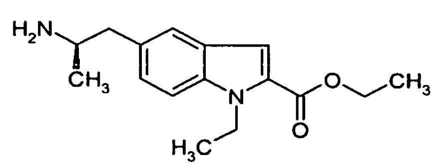
^{1}H NMR (400 MHz, CD_3OD) : δ 7.44-7.39 (2H, m), 7.25 (1H, s), 7.16-7.00 (3H, m), 6.72 (1H, d), 4.99-4.96 (1H, m), 4.64-4.56 (2H, m), 4.02 (3H, s), 3.60-3.54 (1H, m), 3.13-2.89 (4H, m), 1.27-1.26 (3H, m), 0.72 (9H, s), -0.04 (3H, s), -0.24 (3H, s).
LRMS (ESI) : m/z $[M+H]^+$ 513, $[M+Na]^+$ 535.

Preparation 22 : Ethyl 1-ethyl-5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-2-carboxylate hydrochloride



Prepared using the method described for Preparation **11** giving the title compound as a a 4:1 mixture of diastereomers (R,R major). The crude material was treated with excess HCl in MeOH and then crystallised from DIPE / MeOH to give the R,R isomer (d.e.>98% as determined by ^{1}H NMR).
^{1}H NMR (400 MHz, CD_3OD) : δ 7.57-7.45 (7H, m), 7.24 (1H, s), 7.07 (1H, d), 4.68-4.63 (3H, m), 4.40 (2H, q), 3.52-3.44 (1H, m), 3.29-3.25 (1H, m), 2.78-2.72 (1H, m), 1.74 (3H, d), 1.44 (3H, t), 1.37 (3H, t), 1.24 (3H, d).
LRMS (ESI) : m/z $[M+H]^+$ 379, $[M+Na]^+$ 401.

Preparation 23 : Ethyl 1-ethyl-5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate

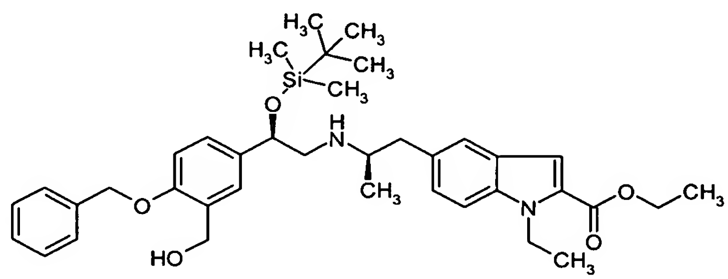


Prepared using the amine from Preparation **22** and the method described for Preparation **9**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.46-7.41 (2H, m), 7.20-7.18 (2H, m), 4.61 (2H, q), 4.35 (2H, q), 3.17-3.09 (1H, m), 2.77-2.64 (2H, m), 1.39 (3H, t), 1.34 (3H, t), 1.10 (3H, d).

LRMS (ESI) : m/z $[M+H]^+$ 275, $[M+Na]^+$ 297.

Preparation 24 : Ethyl 1-ethyl-5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxy methyl)phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]propyl}-1*H*-indole-2-carboxylate

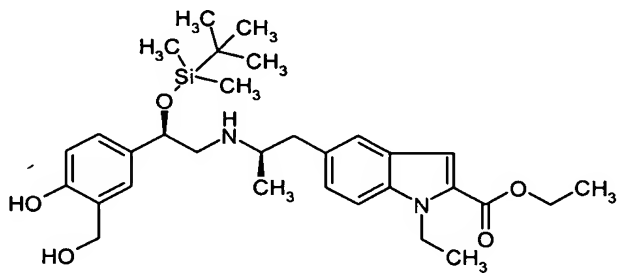


Prepared using the amine from Preparation **23**, and the bromide from preparation **15** and the method described for Preparation **8**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.43-7.29 (8H, m), 7.19 (1H, s), 7.11 (1H, d), 6.99 (1H, d), 6.74 (1H, d), 5.00 (2H, s), 4.73-4.70 (1H, m), 4.61-4.56 (4H, m), 4.30 (2H, q), 3.00-2.88 (2H, m), 2.78-2.61 (3H, m), 1.37-1.31 (6H, m), 1.11 (3H, d), 0.73 (9H, s), -0.08 (3H, s), -0.24 (3H, s).

LRMS (ESI) : m/z $[M+H]^+$ 645, $[M+Na]^+$ 667.

Preparation 25 : Ethyl 1-ethyl-5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylate

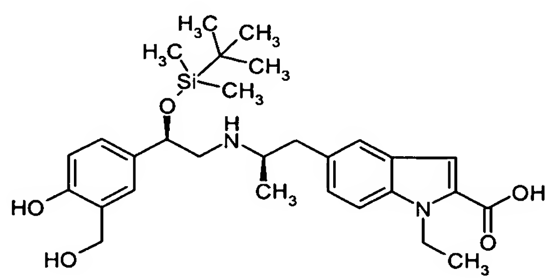


Prepared using the amine from Preparation **24** and the method described for Preparation **7**.

^{1}H NMR (400 MHz, CD_3OD) : δ 7.38-7.35 (2H, m), 7.19-7.09 (3H, m), 6.96 (1H, d), 6.64 (1H, d), 4.68-4.58 (5H, m), 4.37 (2H, q), 2.98-2.60 (5H, m), 1.41 (3H, t), 1.36 (3H, t), 1.10 (3H, d), 0.72 (9H, s), -0.09 (3H, s), -0.25 (3H, s).

LRMS (ESI) : m/z $[M+H]^+$ 555, $[M+Na]^+$ 577.

Preparation 26 : 1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylic acid

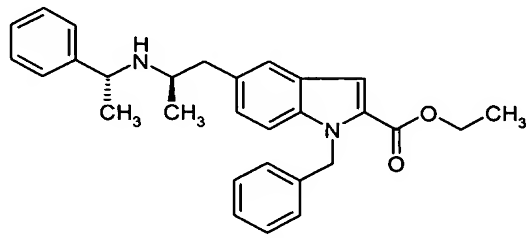


Prepared using the amine from Preparation **25** and the method described for Preparation **6**.

^{1}H NMR (400 MHz, CD_3OD) : δ 7.41-7.35 (2H, m), 7.21 (1H, bs), 7.07-6.95 (3H, m), 6.67 (1H, d), 4.94-4.91 (1H, m), 4.60-4.55 (4H, m), 3.54-3.49 (1H, m), 3.09-2.84 (4H, m), 1.27-1.21 (6H, m), 0.67 (9H, s), -0.09 (3H, s), -0.29 (3H, s).

LRMS (ESI) : m/z $[M+H]^+$ 527, $[M+Na]^+$ 549.

Preparation 27 : Ethyl 1-benzyl-5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino} propyl)-1*H*-indole-2-carboxylate hydrochloride

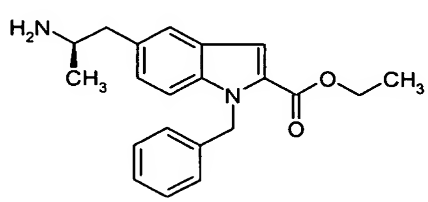


Prepared using the method described for Preparation **11** giving the title compound as a a 4:1 mixture of diastereomers (R,R major). The crude material was treated with excess HCl in MeOH and then crystallised from DIPE / MeOH to give the R,R isomer (d.e.>98% as determined by ^{1}H NMR).

^{1}H NMR (400 MHz, CD_3OD) : δ 7.51-7.45 (6H, m), 7.37 (1H, d), 7.30 (1H, s), 7.22-7.16 (3H, m), 7.01-6.97 (3H, m), 5.84 (2H, s), 4.59 (1H, q), 4.31 (2H, q), 3.42-3.38 (1H, m), 3.28-3.19 (1H, m), 2.75-2.70 (1H, m), 1.69 (3H, d), 1.33 (3H, t), 1.20 (3H, d).

LRMS (ESI) : m/z $[M+H]^+$ 441.

Preparation 28 : Ethyl 1-benzyl-5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate

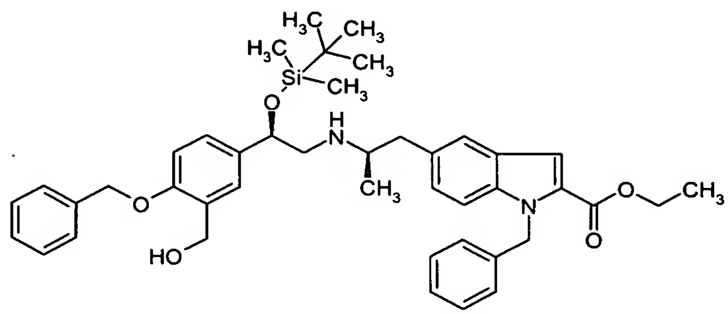


Prepared using the amine from Preparation **27** and the method described for Preparation **9**.

^{1}H NMR (400 MHz, CD_3OD) : δ 7.55 (1H, s), 7.41 (1H, d), 7.36 (1H, s), 7.28-7.20 (4H, m), 7.05 (2H, d), 5.89 (2H, s), 4.35 (2H, q), 3.20-3.14 (1H, m), 2.82-2.69 (2H, m), 1.38 (3H, t), 1.15 (3H, d)

LRMS (ESI) : m/z $[M+H]^+$ 337.

Preparation 29 : Ethyl 1-benzyl-5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl) phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino] propyl}-1*H*-indole-2-carboxylate

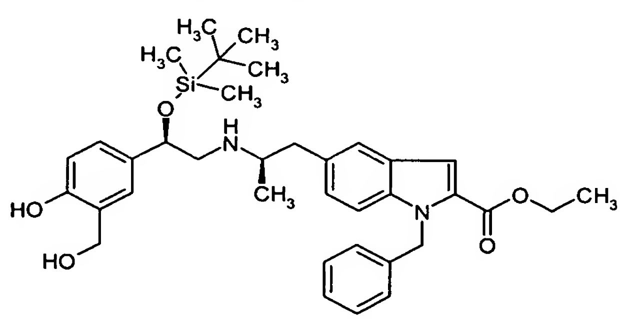


Prepared using the amine from Preparation **26**, and the bromide from preparation **15** and the method described for Preparation **8**.

^{1}H NMR (400 MHz, CD_3OD) : δ 7.47-7.34 (10H, m), 7.27-7.19 (3H, m), 7.13-7.00 (3H, m), 6.75 (1H, d), 5.86 (2H, s), 5.02 (2H, s), 4.78-4.75 (1H, m), 4.71-4.69 (2H, m), 4.33-4.24 (2H, m), 3.05-2.91 (2H, m), 2.83-2.78 (1H, m), 2.71-2.66 (2H, m), 1.33 (3H, t), 1.16 (3H, d), 0.79 (9H, s), -0.03 (3H, s), -0.19 (3H, s).

LRMS (ESI) : m/z $[M+H]^+$ 707.

Preparation 30 : Ethyl 1-benzyl-5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylate

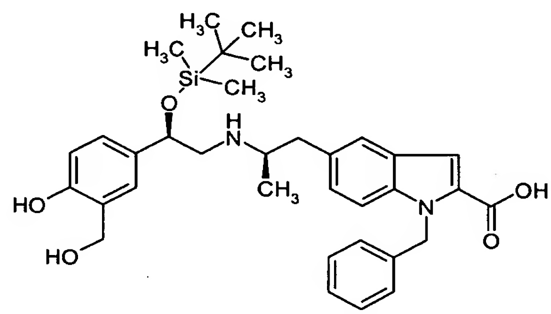


Prepared using the ester from Preparation **29** and the method described for Preparation **7**.

^{1}H NMR (400 MHz, CD_3OD) : δ 7.41 (1H, bs), 7.29-6.95 (10H, m), 6.65 (1H, d), 5.82 (2H, s), 4.69-4.66 (1H, m), 4.62-4.55 (2H, m), 4.31 (2H, q), 2.98-2.85 (2H, m), 2.71-2.60 (3H, m), 1.34 (3H, t), 1.08 (3H, d), 0.72 (9H, s), -0.10 (3H, s), -0.25 (3H, s).

LRMS (ESI) : m/z $[M+H]^+$ 617.

Preparation 31 : 1-Benzyl-5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylic acid

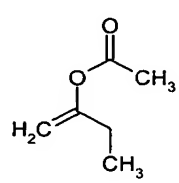


Prepared using the ester from Preparation **30** and the method described for Preparation **6**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.56 (1H, bs), 7.43-703 (10H, m), 6.80 (1H, m), 5.95 (2H, s), 5.07-5.04 (1H, m), 4.73-4.64 (2H, m), 3.68-3.61 (1H, m), 3.23-2.95 (4H, m), 1.33 (3H, d), 0.81 (9H, s), 0.04 (3H, s), -0.15 (3H, s).

LRMS (ESI) : m/z $[M+H]^+$ 589.

Preparation 32: Acetic acid 1-methylene-propyl ester

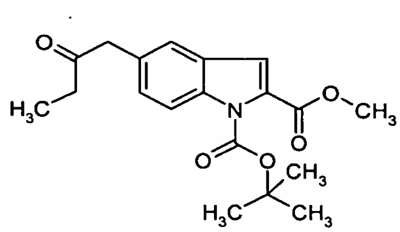


But-1-yne (13.5 g, 0.25 mol) was added to a solution of mercuric acetate (1.2 g, 4.6 mmol) and boron trifluoride dietherate (1.68 g, 11.8 mmol) in acetic

anhydride (40 ml) at –10 °C. After stirring for 3 h, the solution was left at –20 °C overnight. The reaction mixture was added to a cooled (0 °C) 6.6 M solution of sodium hydroxide (150 ml). Diethyl ether (150 ml) was then added and the mixture stirred for 1 h. The etheral layer was separated and washed with brine and dried (Na_2SO_4). The product was purified by distillation (120 °C) to yield a clear oil (4.5 g).

^1H NMR (400 MHz, CD_3OD) : δ 4.75 (2H, 2xs), 2.20 (2H, q), 2.18 (3H, s), 1.05 (3H, t).

<u>Preparation 33 : 1-*tert*-Butyl 2-methyl 5-(2-oxobutyl)-1*H*-indole-1,2-dicarboxylate</u>

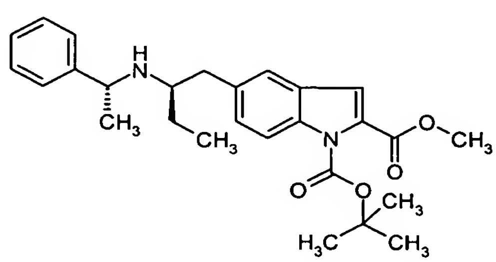


Prepared using the bromide from Preparation **13**, the ester from preparation **32** and the method described for Preparation **12**.

^1H NMR (400 MHz, $CDCl_3$) : δ 8.03 (1H, d), 7.44 (1H, s), 7.25 (1H, d partially obscured by solvent), 7.05 (1H, s), 3.92 (3H, s), 3.77 (2H, s), 2.48 (2H, q), 1.62 (9H, s), 1.03 (3H, t).

LRMS (ESI) : m/z $[M+Na]^+$ 368.

<u>Preparation 34 : Methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}butyl)-1*H*-indole-2-carboxylate</u>

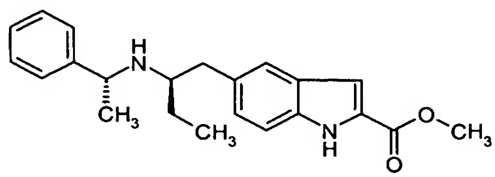


Prepared using the ketone from Preparation **33** and the method described for Preparation **11**.

^{1}H NMR (400 MHz, CD_3OD) : δ 7.90 (1H, m), 7.29-7.23 (4h, m), 7.20-6.82 (4H, m), 3.92 (3H, 2xs), 3.90 (1H, m), 2.89-2.53 (3H,m), 1.62 (9H, s), 1.27 (3h, 2xd), 0.95-0.81 (3H, 2xt).

LRMS (APCI) : m/z $[M+H]^+$ 451.

Preparation 35 : Methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}butyl)-1*H*-indole-2-carboxylate hydrochloride

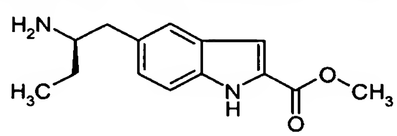


Prepared using the amine from Preparation **34** and the method described for Preparation **10**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.50-7.41 (7H, m), 7.12 (1H, s), 7.03 (1H, d), 4.43 (1H, q), 3.91 (3H, s), 3.31-3.24 (2H, m), 3.15-3.08 (1H, m), 2.98-2.92 (1H, m), 1.67 (3H, d), 1.66-1.51 (1H, m), 0.9 (3H, t).

LRMS (ESI) : m/z $[M+H]^+$ 351.

Preparation 36 : Methyl 5-[(2*R*)-2-aminobutyl]-1*H*-indole-2-carboxylate

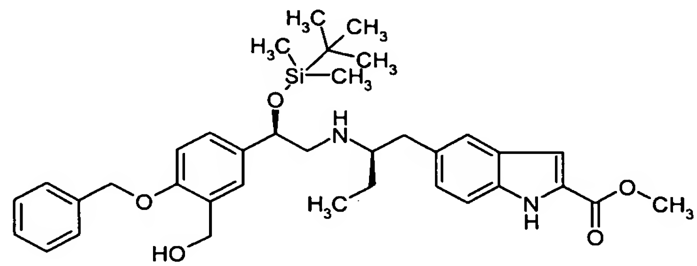


Prepared using the amine from Preparation **35** and the method described for Preparation **9**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (1H, bs), 7.49 (1H, s), 7.34 (1H, d), 7.13-7.15 (2H, m), 3.93 (3H, s), 2.99-2.88 (2H, m), 2.55-2.50 (1H, m), 1.51-1.20 (4H, m), 0.99 (3H, t).

LRMS (ESI) : m/z $[M+H]^+$ 247.

Preparation 37 : Methyl 5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl) phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino] butyl}-1*H*-indole-2-carboxylate

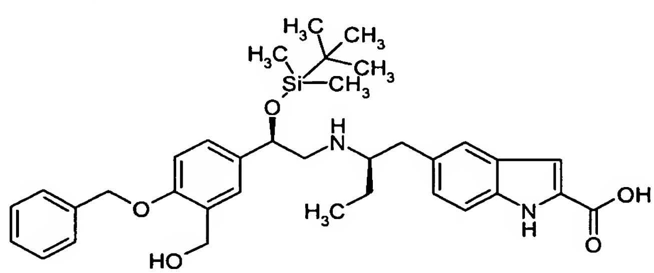


Prepared using the bromide from Preparation **15** the amine from preparation **36** and the method described for Preparation **8**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (1H, bs), 7.60-7.50 (6H, m), 7.44 (1H, s), 7.41-7.26 (4H, m), 6.98 (1H, d), 5.25 (2H, s), 4.95-4.85 (3H, m), 4.08 (3H, s), 3.03-2.80 (5H, m), 1.95-1.55 (4H, m), 1.10 (3H, t), 1.01 (9H, s), 0.18 (3H, s), 0.00 (3H, s).

LRMS (ESI) : m/z $[M+H]^+$ 617.

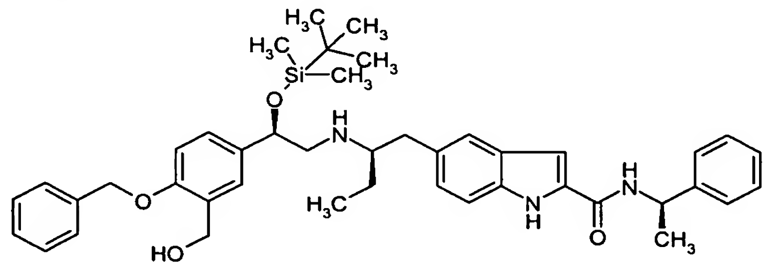
Preparation 38 : 5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino] butyl}-1*H*-indole-2-carboxylic acid



Preparation **37** (790 mg, 1.28 mmol) and LiOH (1 M in water, 2.56 ml) in THF (40 ml) and water (6 ml) were stirred at RT overnight. The solvent was removed *in vacuo* to yield a yellow foam (870 mg).

LRMS (APCI) : m/z $[M+H]^+$ 603.

Preparation 39 : 5-[(2*R*)-2-({(2*R*)- 2-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethyl}amino)butyl]-*N*-[(*1R*)-1-phenylethyl]-1H-indole-2-carboxamide

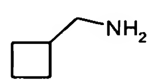


A mixture of Preparation 38 (154 mg, 256 μmol), (1*R*)-1-phenylethylamine (38 mg, 310 μmol), WSCDI (59 mg, 210 μmol), HOBt (38 mg, 280 μmol) and DIPEA (129 mg, 1.0 mmol) in DMF at RT overnight. The solvent was removed *in vacuo* and the material taken up in EtOAc, washed with water, brine. The product was purified by chromatography (2-4 % MeOH in CH_2Cl_2 +0.3 % NH_3) to yield a colourless foam (153 mg).

^{1}H NMR (400 MHz, CD_3OD) : δ 7.27-7.41 (12H, m), 7.20 (1H, m), 7.14 (1H, s), 6.92-7.00 (2H, d), 6.65 (1H, d), 5.24 (1H, q), 5.01 (2H, s), 4.60-4.70 (3H, m), 2.56-2.89 (5H, m), 1.62-1.52 (4H, m), 1.43 (1H, m), 0.97 (3H, t), 0.74 (9H, s), -0.08 (3H, s), -0.26 (3H, s).

LRMS (ESI) : m/z $[M]^+$ 706.

Preparation 40 : Cyclobutylmethylamine

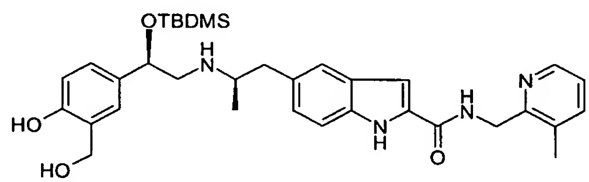


Borane (1M in THF, 68 ml, 67.8 mmol) was added dropwise to a cooled (0 °C) solution of cyclobutylnitrile (5.0 g, 61.6 mmol) in THF (7 ml) under nitrogen. The mixture was allowed to warm to RT and heated to reflux for 17 h. The mixture was then cooled to 0 °C and quenched by the addition of MeOH (81 ml). The mixture was allowed to warm to RT and the solvent removed. The material was re-dissolved in MeOH (50 ml) and acidified with conc. HCl (50 ml) before being heated to reflux for 2 h. The solvents were removed and the residue triturated with Et_2O and the white powder filtered off (4.51 g).

[1]H NMR (400 MHz, CD_3OD) : δ 2.95 (2H, d), 2.76 (1H, m), 2.15 (2H, m), 2.05-1.75 (4H, m),

Analysis : Found C 47.17; H 9.84; N 11.05; $C_5H_{11}N_1$.HCl 0.3 $2H_2O$ requires C 47.28; H 10.00; N 11.03.

Preparation 41 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxy methyl)phenyl]ethyl}amino)propyl]-*N*-(3-methyl-pyridin-2-ylmethyl)-1*H*-indole-2-carboxamide

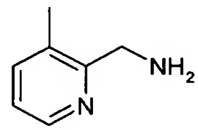


A solution of preparation **6** (200 mg, 400 μmol) in DMF (3 ml) was treated with *O*-benzotriazol-1-yl-*N, N, N', N'*-tetrauronium hexafluororphosphate (94 mg, 400 μmol), DIPEA (0.14 ml, 800 μmol) and stirred at RT for 30 min. preparation **42** (49 mg, 400 mmol) in DMF (1 ml) and the solution stirred at 50 °C for 18 h. The solvent was removed *in vacuo* and the crude material dissolved in ethyl acetate (30 ml) and washed with water (20 ml) and dried (Na_2SO_4). The material was purified by chromatography (0-6 % MeOH in CH_2Cl_2 + 0.3 % NH_3) to yield a green oil which was suspended in diethyl ether and evaporated to yield a white green solid (54 mg).

[1]H NMR (400MHz, CD_3OD): δ 9.18 (1H, s), 8.42 (1H, d), 8.10 (1H, m), 7.50 (1H, d), 7.15 (2H, m), 6.80-7.00 (3H, m), 6.80 (1H, s), 6.60 (1H, d), 4.70-4.90 (5H, m), 2.50-3.10 (5H, m), 2.30 (3H, s), 1.20 (3H, d), 0.80 (9H, s), -0.10 (3H, s), -0.30 (3H, s)

HRMS : $C_{34}H_{47}N_4O_4Si$ requires : 603.3368 found 603.3365 $[M+H]^+$.

Preparation 42 : (3-Methyl-pyridin-2-yl)methylamine



3-Methylpyridine-2-carbonitrile (2.0 g, 16.95 mmol) in THF (50 ml) at 0 °C was added to a solution of lithium aluminium hydride (16.95 ml, 1 M in THF) and the mixture allowed to warm to RT overnight. The reaction was cooled to 0 °C and quenched with ethyl acetate (2.5 ml). Sodium hydroxide (2.5 ml, 1M) was added and the mixture stirred at RT for 1 h, then filtered through Celite ®. The filtrate was extracted with ethyl acetate (2x 20 ml) and the combined organics washed with brine (50 ml) and dried ($MgSO_4$). The crude material was purified by chromatography (0-5 % MeOH in CH_2Cl_2 + 1 % NH_3) to yield a yellow oil (282 mg).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.39 (1H, d), 7.45 (1H, d), 7.12 (1H, dd), 3.50-4.50 (2H, bs), 4.07 (2H, s), 2.29 (3H, s).

LRMS (ESI) : m/z $[MH]^+$ 123, 145 $[M+Na]^+$.

***In vitro* activity of the indole derivatives of formula (1)**

The ability of the indole derivatives of the formula (1) to act as potent β2 agonists therefore mediating smooth muscle relaxation may be determined by the measure of the effect of beta-2 adrenergic receptor stimulation on electrical field stimulated-contraction of guinea pig trachea strips.

Guinea-pig trachea

Male, Dunkin-Hartley guinea pigs (475-525g) are killed by CO_2 asphyxiation and exsanguination from the femoral artery and the trachea is isolated. Four preparations are obtained from each animal, starting the dissection immediately below the larynx and taking 2.5 cm length of trachea. The piece of trachea is opened by cutting the cartilage opposite the trachealis muscle, then transverse sections, 3-4 cartilage rings wide, are cut. The resulting strip preparations are suspended in 5 ml organ baths using cotton threads tied through the upper and lower cartilage bands. The strips are equilibrated, un-tensioned, for 20 minutes

in a modified Krebs Ringer buffer (Sigma K0507) containing 3 μM Indomethacin (Sigma I7378), 10 μM Guanethidine (Sigma G8520) and 10 μM Atenolol (Sigma A7655), heated at 37°C and gassed with 95% O_2/5% CO_2, before applying an initial tension of 1 g. The preparations are allowed to equilibrate for a further 30-45 minutes, during which time they are re-tensioned (to 1 g) twice at 15-minute intervals. Changes in tension are recorded and monitored via standard isometric transducers coupled to a data-collection system (custom-designed at Pfizer). Following the tensioning equilibration, the tissues are subjected to electrical field stimulation (EFS) using the following parameters : 10 s trains every 2 minutes, 0.1 ms pulse width, 10 Hz and just-maximal voltage (25 Volts) continuously throughout the length of the experiment. EFS of post-ganglionic cholinergic nerves in the trachea results in monophasic contractions of the smooth muscle and twitch height is recorded. The organ baths are constantly perfused with the above-described Krebs Ringer buffer by means of a peristaltic pump system (pump flow rate 7.5 ml / minute) throughout the experiment, with the exception of when a beta-2 agonist according to the present invention is added, the pump is then stopped for the time of the cumulative dosing to the bath and started again after maximal response is reached for the wash-out period.

Experimental protocol for assessment of potency and efficacy

Following equilibration to EFS, the peristaltic pump is stopped and the preparations 'primed' with a single dose of 300 nM isoprenaline (Sigma I5627) to establish a maximal response in terms of inhibition of the contractile EFS response. The isoprenaline is then washed out over a period of 40 minutes. Following the priming and wash-out recovery, a standard curve to isoprenaline is carried out on all tissues (Isoprenaline Curve 1) by means of cumulative, bolus addition to the bath using half log increments in concentration. The concentration range used is 1^{e-9} to $1^{e}/3^{e-6}$ M. At the end of the isoprenaline curve the preparations are washed again for 40 minutes before commencing a second curve, either to isoprenaline (as internal control) or a beta-2 agonist according to the present invention. Beta-2 agonist responses are expressed as percentage inhibition of the EFS response. Data for beta-2 agonist are

normalised by expressing inhibition as a percentage of the maximal inhibition induced by isoprenaline in Curve 1. The EC_{50} value for beta-2 agonist according to the present invention refers to the concentration of compound required to produce half maximal effect. Data for beta-2 agonists according to the present invention are then expressed as relative potency to isoprenaline defined by the ratio (EC_{50} beta-2 agonist)/(EC_{50} Isoprenaline).

Confirmation of beta-2 mediated functional activity

Beta-2 agonist activity of test compounds is confirmed using the protocol above, however, prior to constructing the curve to beta-2 agonist according to the present invention, the preparations are pre-incubated (for a minimum of 45 minutes) with 300 nM ICI 118551 (a selective β_2 antagonist) which results in the case of a beta-2 mediated effect in a rightward-shift of the test compound dose response curve.

According to another alternative, the agonist potency for the $\beta 2$ receptor of the indole derivatives of the formula (1) may also be determined by the measure of the concentration of compound according to the present invention required to produce half maximal effect (EC_{50}) for the $\beta 2$ receptor.

Compound Preparation

10 mM/100% DMSO (dimethylsulfoxide) stock of compound is diluted to required top dose in 4 % DMSO. This top dose is used to construct a 10-point semi-log dilution curve, all in 4 % DMSO. Isoprenaline (Sigma, I-5627) was used as a standard in every experiment and for control wells on each plate. Data was expressed as % Isoprenaline response.

Cell Culture

CHO (Chinese Hamster Ovary) cells recombinantly expressing the human $\beta 2$ adrenergic receptor (from Kobilka et al., PNAS 84: 46-50, 1987 and Bouvier et al., Mol Pharmacol 33: 133-139 1988 CHOhβ2) were grown in Dulbeccos MEM/ NUT MIX F12 (Gibco, 21331-020) supplemented with 10 % foetal bovine serum (Sigma, F4135, Lot 90K8404 Exp 09/04), 2 mM glutamine (Sigma, G7513),

500 µg/ml geneticin (Sigma, G7034) and 10 µg/ml puromycin (Sigma, P8833). Cells were seeded to give about 90 % confluency for testing.

Assay Method

25 µl / well each dose of compound was transferred into a cAMP- Flashplate® (NEN, SMP004B), with 1% DMSO as basal controls and 100 nM Isoprenaline as max controls. This was diluted 1:2 by the addition of 25 µl / well PBS. Cells were trypsinised (0.25% Sigma, T4049), washed with PBS (Gibco, 14040-174) and resuspended in stimulation buffer (NEN, SMP004B) to give $1x10^6$ cells / ml CHOhB2. Compounds were incubated with 50 µl / well cells for 1 hour. Cells were then lysed by the addition of 100 µl / well detection buffer (NEN, SMP004B) containing 0.18 µCi / ml ^{125}I-cAMP (NEN, NEX-130) and plates were incubated at room temperature for a further 2 hours. The amount of ^{125}I-cAMP bound to the Flashplate® was quantified using a Topcount NXT (Packard), normal counting efficiency for 1 minute. Dose-response data was expressed as % Isoprenaline activity and fitted using a four parameter sigmoid fit.

It has thus been found that the indole derivatives of formula (1) according to the present invention that are illustrated in examples 1 to 18 above show a β2 cAMP EC_{50} between 0.03 nM and 0.75 nM.